Antimicrobial Stewardship Collaborative of South Carolina

Guidelines for Acute Cystitis and Pyelonephritis: Outpatient Management in Adults

Urinary symptoms

NO → Do **NOT** treat asymptomatic patients with positive urine cultures*

YES

Acute Cystitis

Defined as: lower urinary symptoms/signs (e.g. dysuria, new or increased frequency or urgency, suprapubic tenderness), pyuria on urinalysis, and temperature <38° C

Uncomplicated Cystitis

Defined as:

- Female of childbearing potential
- No urologic abnormalities

Nitrofurantoin (Macrobid)[1]
100 mg PO Q12h x 5 days
ONLY if CrCl ≥30 mL/min

OR

Fosfomycin[2]
3 G PO x 1 dose

OR

Trimethoprim/sulfamethoxazole (SMX/TMP)[3]
1 DS PO Q12h x 3 days

Avoid SMX/TMP if SMX/TMP use or prior urinary culture with SMX/TMP-resistant bacteria within 12 months

Complicated Cystitis

Defined as:

- >2 UTIs in past 12 months
- Urologic abnormalities (e.g. stones)
- Males
- Indwelling catheters

Nitrofurantoin (Macrobid)
100 mg PO Q12h x 7 days
ONLY if CrCl ≥30 mL/min[1]

OR

Trimethoprim/sulfamethoxazole (SMX/TMP)
1 DS PO Q12h x 7 days[3]

Avoid SMX/TMP if SMX/TMP use or prior urinary culture with SMX/TMP-resistant bacteria within 12 months

Acute Pyelonephritis

Defined as: fever >38° C, unilateral back or flank pain, costovertebral angle tenderness ± radiologic evidence of kidney involvement

Risk factors for fluoroquinolone resistance

(Any of the following)

- Use of fluoroquinolones in the past 12 months
- Outpatient gastrointestinal or genitourinary procedure in past 30 days
- Resident of a nursing home/skilled nursing facility

NO

Levofloxacin[4]
750 mg PO Q24h x 5 days ♀
or 14 days ♂

OR

Ciprofloxacin[5]
500 mg PO Q12h x 7 days ♀
or 14 days ♂

YES

Ceftriaxone 1g IV/IM x 1
PLUS
SMX/TMP[3]
1 DS PO Q12h x 14 days

Avoid SMX/TMP if SMX/TMP use or prior urinary culture with SMX/TMP-resistant bacteria within 12 months

[1] Nitrofurantoin should be AVOIDED in patients with creatinine clearance <30 mL/min.
[2] Fosfomycin is not recommended as a first-line therapy in patients with complicated disease. If used for complicated cystitis, should repeat Q72h for 2-3 doses.
[3] If CrCl <30 mL/min, administer SMX/TMP 1 SS PO Q12h. SMX/TMP should be used with caution in pregnant females.
[4] If CrCl <20-49 mL/min, administer 750 mg Q48h, and if <20 mL/min, administer 750 mg followed by 500 mg Q48h.
[5] If CrCl <30 mL/min, administer ciprofloxacin 250 mg Q12h.

Diagnosis:

- Urinalysis and urine culture should be obtained prior to initiating antibiotics in patients with recurrent infections, urologic abnormalities, pregnancy, and in males.
- Urinalysis, urine culture, and blood cultures should be obtained prior to initiating antibiotics in patients with acute pyelonephritis, when feasible.
- For patients with indwelling catheters in place for > 2 weeks from onset of symptoms, catheter should be replaced prior to obtaining urinalysis and urine culture. If possible, catheter should be discontinued, and a culture of a voided midstream urine specimen should be obtained.
- Consider imaging in males and patients with recurrent urinary infections.
- Presence of pyuria on urinalysis without symptoms does not indicate a urinary tract infection. Absence of pyuria is indicative that a urinary tract infection is not present with the exception of acute pyelonephritis with complete uretic obstruction.
- Patients with non-specific symptoms:
  - Change in urine color, odor, or turbidity are typically due to dehydration and not indicators for urinalysis or urine culture.
  - Behavioral changes including worsening mental or functional status do not on their own indicate a urinary tract infection. These patients should be monitored and encouraged to have increased fluid intake, if possible. Other causes of mental status change should be assessed including constipation, dehydration, electrolyte abnormalities, medications (e.g. narcotics, etc.), liver failure, renal failure, blood sugar issues, sleep deprivation, stroke, and other infections.
- Urine cultures should not be done after treatment of cystitis or pyelonephritis to document cure.

Treatment:

- **Asymptomatic Bacteriuria**

  *Treatment of asymptomatic bacteriuria is strongly discouraged because antibiotics may lead to harmful effects to patient (e.g. *Clostridium difficile* infection, induction of antimicrobial resistance, etc.) that cannot be justified based on lack of any treatment benefits. The only exceptions are: pregnant women and before transurethral resection of the prostate or other urologic procedures for which mucosal bleeding is anticipated.

- **Acute Cystitis**
  - Fluoroquinolone (ciprofloxacin, levofloxacin) use is strongly discouraged for the treatment of acute cystitis because the risk of harmful adverse effects (e.g. *C. difficile* infection; tendonitis; neurotoxicity; QTc prolongation; induction of antimicrobial resistance) exceeds potential benefit.
  - Similarly, oral 3rd generation cephalosporins (e.g. cefdinir, cefpodoxime) should be AVOIDED due to low urinary concentrations and high risk of adverse events, including induction of antimicrobial resistance.
  - **Alternative oral regimens for cystitis:**
    - Contraindications to first-line therapy
      - In patients with contraindications to all first-line therapies (e.g. complicated cystitis AND CrCl <30 mL/min AND SMX/TMP allergy), cephalexin 500 mg PO Q8h or amoxicillin/clavulanic acid 500 mg/125 mg PO Q12h for 7-10 days may be used.
      - Fluoroquinolones are considered only as last resort options in patients with cystitis in the absence of risk factors for fluoroquinolone resistance. May use ciprofloxacin 250 mg PO Q12h x 3 days.

- Extended-spectrum β–lactamase (ESBL)-producing Bacteria
  - Non-β-lactam antibiotics (nitrofurantoin, fosfomycin and SMX/TMP) often retain activity against ESBL-producing *Enterobacteriaceae* if not previously used and may be considered therapeutic options for suspected cystitis due to ESBL-producing *Enterobacteriaceae*. Fosfomycin should be given 3 G PO Q72h x 3 doses.
- Vancomycin-resistant *Enterococcus* (VRE)
  - Growth of VRE in a urine culture often indicates urinary colonization due to recent use of antibiotics, rather than a urinary infection. However, when treatment is indicated in symptomatic patients, fosfomycin retains good activity and may be considered a therapeutic option for suspected cystitis due to VRE. Fosfomycin should be given 3 G PO Q72h x 2 doses.

Acute Pyelonephritis

- Nitrofurantoin and fosfomycin should be AVOIDED in patients with suspected of documented pyelonephritis. These antibiotics do not concentrate outside the urine, including the interstitial cells of the kidney.
- Use of oral 3rd generation cephalosporins (e.g. cefdinir, cefpodoxime) is highly discouraged due to low urinary concentrations and higher risk of treatment failure in comparison to fluoroquinolones and SMX/TMP.
- If a patient meets any of the criteria for fluoroquinolone resistance, but SMX/TMP cannot be used due to allergy or high risk of resistance:
  - Consider oral ciprofloxacin or levofloxacin following ceftriaxone 1g IV/IM dose as long as patient has only one risk factor for fluoroquinolone resistance and prior fluoroquinolone use was within the past 3-12 months. Estimated probability of fluoroquinolone resistance is 20-40%. Urine culture would need follow-up.
  - Patients with fluoroquinolones use within the past 3 months or multiple risk factors for resistance have >50% probability of pyelonephritis due to fluoroquinolone-resistant bacteria. Fluoroquinolone empirical therapy is discouraged in this group. There are currently insufficient data to recommend alternative oral antibiotics for acute pyelonephritis in these patients. Observation/admission may be considered while receiving IV ceftriaxone, awaiting blood and urine culture results.

References:

1) Gupta K, Hooten TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis* 2011;52:e103-20.
2) Nicolle LE, Bradley S, Colgan R, et al. Infectious Diseases Society of America Guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clin Infect Dis* 2006;40:643-54.
3) FDA updates warnings for fluoroquinolone antibiotics. U.S. Food & Drug Administration. Released 26 July 2016. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm513183.htm
4) Pichichero ME. Cephalosporins can be prescribed safely for penicillin-allergic patients. *J Fam Pract* 2006;55:106-12.
5) Shah A, Justo JA, Bookstaver PB, et al. Application of fluoroquinolone resistance score in management of complicated urinary tract infections. *Antimicrob Agents Chemother* 2017; 61: e02313-16.
6) Falagas ME, et al. Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum beta-lactamase producing Enterobacteriaceae infections: a systematic review. *Lancet Infect Dis* 2010;10:43-50.
7) Veve MP, et al. Comparison of fosfomycin to ertapenem for outpatient or step-down therapy of extended-spectrum beta-lactamase urinary tract infection. *Int J Antimicrob Agents* 2016;48:56-60.
8) Sanasi-Bhola K, et al. Fosfomycin in vitro activity against extended spectrum beta-lactamase positive and carbapenem resistant Enterobacteriaceae urine isolates. Presented at IDWeek 2014. Abstract #40851.
9) Hayes JE, O'Quinn B, Lu K, et al. Fosfomycin resistance among vancomycin-resistant enterococcal isolates at a tertiary care medical center. Presented at *American College of Clinical Pharmacy*; 2016; Abstract #176.
10) Hoang P, Salbu RL. Updated nitrofurantoin recommendations in the elderly: a closer look at the evidence. *Consult Pharm* 2016 Jul;31:381-4.
11) Nieuwkoop C, van der Starre WE, Stalenhoef JE, et al. Treatment duration of febrile urinary tract infection: a pragmatic randomized, double-blind, placebo-controlled non-inferiority trial in men and women. *BMC Medicine* 2017;15:70.
12) Johnson JR, Russo TA. Acute pyelonephritis in adults. N Engl J Med. 2018 Jan 4;378(1):48-59.