

## Treating UTIs with the Tried and True

Kate Unterberger, Pharm.D. Candidate 2016 and Andrew Gibler, Pharm.D., Oregon State University College of Pharmacy Drug Use Research and Management

Symptomatic urinary tract infections (UTIs) are the most frequent bacterial infection diagnosed by outpatient providers, and one of the most common indications for antibiotic prescriptions every year.<sup>1,2</sup> Despite availability of clinical practice guidelines, UTIs are commonly not managed appropriately.<sup>3-5</sup> Recent evidence suggests that in most cases, shorter courses of antibiotics are equally as effective as longer regimens, are associated with fewer adverse events, and have less potential to promote antibiotic resistance.<sup>6-8</sup> For adults eligible for outpatient management with oral antibiotics, a shorter course of treatment may be best.

### Uncomplicated UTIs

Bacteria commonly implicated in uncomplicated cystitis and pyelonephritis are listed in Table 1. *Escherichia coli* remains the most common pathogen and accounts for 75-95% of infections in women.<sup>2,9</sup> Other gram-negative bacteria associated with UTIs include *Proteus mirabilis* and *Klebsiella* species.<sup>9</sup> Although gram-positive bacteria are less commonly associated with uncomplicated UTIs, *Staphylococcus saprophyticus* is associated with 5% to 15% of UTIs, most of which are cases of cystitis in younger women.<sup>9</sup>

**Table 1. Pathogens Commonly Implicated in Uncomplicated Cystitis and Pyelonephritis<sup>3,7</sup>**

<i>Escherichia coli</i> *	<i>Klebsiella pneumoniae</i>
<i>Staphylococcus saprophyticus</i>	<i>Proteus mirabilis</i>

\*Accounts for 75%-95% of all UTIs

### Uncomplicated Cystitis

UTIs are considered uncomplicated in otherwise healthy, non-pregnant premenopausal women without urinary tract abnormalities.<sup>2,10,11</sup> Cystitis, which affects the bladder and urethra, is a diagnosis typically based on patient-reported symptoms.<sup>1,3</sup> Cystitis rarely develops into pyelonephritis and can be successfully cured with only a few days of antibiotic treatment (Table 2).<sup>2</sup>

**Table 2. Antibiotic Recommendations for Uncomplicated Cystitis<sup>2,3,9,12</sup>**

	Drug	Dose	Days
First-line therapy	Nitrofurantoin ( <i>Macrobid</i> )	100 mg BID	5
	TMP-SMX ( <i>Bactrim DS, Septra DS</i> )	160/800 mg BID	3
Second-line therapy	Ciprofloxacin ( <i>Cipro</i> )	250 mg BID	3
	Levofloxacin ( <i>Levaquin</i> )	250 mg Daily	3
	Fosfomycin ( <i>Monurol</i> )	3 grams Once	1

Abbreviations: BID, twice daily; mg, milligrams; TMP-SMX, trimethoprim-sulfamethoxazole.

The Infectious Disease Society of America (IDSA) recommends either nitrofurantoin or trimethoprim-sulfamethoxazole (TMP-SMX) as first-line therapy for acute uncomplicated cystitis, though local antibiograms can be helpful to guide empiric therapy.<sup>3,13</sup> TMP-SMX has long been considered first-line therapy in the United States, and is very effective against susceptible pathogens. However, increasing rates of resistance have caused the IDSA to modify their recommendation to apply only to cases in which local resistance rates to TMP-SMX do not exceed 20%.<sup>3</sup> Antibiograms from local Portland hospitals report that about 78% of *Escherichia coli* pathogens cultured from infected patients are susceptible to TMP-SMX.<sup>14,15</sup> The most appropriate antibiotic for uncomplicated cystitis may also depend on patient antibiotic and medical history, potential for adverse drug effects, drug interactions and cost.<sup>13</sup>

Clinical trial results demonstrate a 5-day course of nitrofurantoin has comparable efficacy to a 3-day course of TMP-SMX for treating acute uncomplicated cystitis.<sup>10</sup> Nitrofurantoin is an appropriate alternative antibiotic because resistance rates continue to remain low. It is indicated exclusively for UTIs, specifically in women, because therapeutic concentrations are only achieved in the urine. Nitrofurantoin is a reasonable option for patients on warfarin since the drug-drug interaction is less pronounced than with TMP-SMX or fluoroquinolones. However, it should be avoided in patients with renal impairment (creatinine clearance less than 60 mL/min), and it is not recommended for UTI treatment in men due to inferior tissue penetration.<sup>2</sup>

Fluoroquinolones, such as ciprofloxacin and levofloxacin, should generally be avoided in treatment of relatively benign infections such as uncomplicated UTIs, though they have demonstrated good efficacy for treating uncomplicated cystitis.<sup>2</sup> Fluoroquinolones are especially susceptible to antibiotic resistance, and should be reserved for more serious infections that have fewer treatment options.<sup>3</sup> However, contrary to these guideline recommendations, fluoroquinolones continue to be the most frequently prescribed antibiotics in the U.S. for treatment of outpatient UTIs.<sup>5</sup>

Fosfomycin, administered as a single 3-gram dose, is another treatment option for uncomplicated cystitis. It has shown little resistance, but it is more expensive and may have inferior efficacy compared to other treatments.<sup>3</sup> Fosfomycin may be a more appropriate choice in areas known to have higher levels of antibiotic resistance to other therapies.

### Uncomplicated Pyelonephritis

UTIs that affect the kidneys are classified as pyelonephritis, and although some cases result in hospital admission, most can be treated in the outpatient setting (Table 3). Symptoms more indicative of acute uncomplicated pyelonephritis include flank pain, costovertebral angle tenderness (Murphy's punch sign or Pasternacki's sign), fever, nausea, and vomiting.<sup>7,12</sup> Unlike cystitis, diagnosis normally involves a urinalysis.<sup>3,12</sup> Urine culture and susceptibilities should guide antibiotic treatment, but fluoroquinolones are often recommended for empiric treatment in regions where resistance to fluoroquinolones does not exceed 10%.<sup>2,3,9</sup> In the Portland area, about 85% of *E. coli* isolates are susceptible to fluoroquinolones,<sup>14,15</sup> so the patient's medical history is an important consideration.

**Table 3. Oral Antibiotic Recommendations for Acute Uncomplicated Pyelonephritis<sup>2,3,9,12</sup>**

Drug	Dose	Days
Ciprofloxacin (Cipro)	500 mg BID	7
Levofloxacin (Levaquin)*	500 mg Daily	7
TMP-SMX (Bactrim DS, Septra DS)	160/800 mg BID	14

Abbreviations: BID, twice daily; mg, milligrams; TMP-SMX, trimethoprim-sulfamethoxazole  
\*Infectious Diseases Society of America also recommends 750 mg daily for 5 days as an option.

Due to the growing presence of antibiotic resistance, several studies have been performed to evaluate the optimal duration of antibiotic treatment for acute uncomplicated pyelonephritis.<sup>6-8</sup> Results suggest that a 7-day course of ciprofloxacin is equally effective as a 14-day course in terms of cure rates.<sup>6</sup> Likewise, a 7-day course of ciprofloxacin appears to have superior bacteriologic and clinical cure rates compared to a 14-day TMP-SMX regimen.<sup>7</sup>

**Complicated UTIs**

More pathogens are implicated in complicated UTIs. Even though *E. coli* and other enterobacteriaceae, such as *Klebsiella*, *Proteus*, and *Enterobacter*, still cause the majority of infections, cultures of complicated UTIs can also reveal *Pseudomonas*, *Enterococcus*, and *Staphylococcus* species.<sup>12</sup>

Little evidence exists to support treatment recommendations for complicated cystitis and pyelonephritis. Complicated UTIs are associated with a co-morbid condition or urinary tract abnormality, examples of which can be found in Table 4.<sup>12</sup>

**Table 4. Example Criteria for Complicated UTI Classification<sup>9</sup>**

Pregnancy
Diabetes mellitus
Male gender
Immunosuppression with immunosuppressive medications
Functional urinary tract abnormality: indwelling catheter, neurogenic bladder, others
Structural urinary tract abnormality: kidney stones, fistula, polycystic kidney disease, kidney transplant, others

All UTIs in males are considered complicated. Most cases resolve after 7 days with a fluoroquinolone or TMP-SMX, though some conditions such as acute prostatitis may require at least 14 days of treatment.<sup>9,12</sup>

Likewise, UTIs that occur during pregnancy are considered complicated. Amoxicillin, amoxicillin/clavulanate, nitrofurantoin, fosfomycin, or cephalixin are reasonable oral antibiotics for the outpatient treatment of acute UTI during pregnancy.<sup>12</sup> TMP-SMX should be avoided during the 1<sup>st</sup> trimester because of potential risk for neural tube defects.<sup>12</sup> Fluoroquinolone antibiotics lack evidence for safety during pregnancy and should be avoided entirely.

Treatment duration varies by complication, but usually lasts 7 to 14 days.<sup>11,12</sup> Table 4 shows oral antibiotics that are commonly used for outpatient treatment of complicated UTIs.<sup>16</sup>

**Table 5. Oral Antibiotic Treatment Options for Complicated UTIs<sup>12,16</sup>**

Fluoroquinolones: ciprofloxacin (Cipro) or levofloxacin (Levaquin)
Broad spectrum Beta-lactams: amoxicillin/clavulanate (Augmentin), cefdinir (Omnicef), or ceftibuten (Cedax)
Trimethoprim-sulfamethoxazole (Bactrim DS, Septra DS)

**Evidence Suggests Shorter is Better**

As antibiotic resistance continues to increase, treating infections with the shortest effective duration becomes increasingly important. Shortening the duration of antibiotic therapy not only reduces resistance, but also reduces risk of adverse drug events and decreases cost of therapy.<sup>17</sup>

Serious adverse drug events, including *Clostridium difficile* infection, occur more frequently with prolonged use of antibiotics.<sup>18</sup> Risk of infection increases with use of broad-spectrum antibiotics, many of which are easy and effective choices for UTI treatment. Similarly, in the trial that demonstrated equivalent results in 7-day and 14-day regimens of ciprofloxacin for uncomplicated pyelonephritis, symptomatic *Candida* overgrowth was observed more frequently in patients who received the 14-day course.<sup>6</sup> Other notable risks associated with these antibiotics include prolonged QT-interval and tendon rupture with fluoroquinolones; photosensitivity and hyperkalemia with TMP-SMX; and vaginitis with fosfomycin.<sup>13,16,19</sup>

**Conclusion**

The evidence clearly shows shorter courses of antibiotics for acute treatments of uncomplicated UTIs are as effective as longer courses. Furthermore, using the shortest effective course of antibiotics is a public health priority: naturally,

risk of adverse effects increases as the duration of antibiotic therapy increases; but also, overuse promotes widespread antibiotic resistance.

Local antibiograms can be helpful tools for guiding antibiotic selection. TMP-SMX remains an important first-line agent for uncomplicated cystitis, but local resistance rates are around 20%.<sup>14,15</sup> Fluoroquinolones are very effective at treating uncomplicated cystitis, but fluoroquinolones are especially prone to resistance with general use, and therefore should be reserved for pyelonephritis, complicated UTIs, or more serious infections. Nitrofurantoin should be used in female patients with uncomplicated cystitis and normal renal function. Lastly, fosfomycin is expensive but has a unique niche as a single-dose treatment option for uncomplicated cystitis.<sup>3</sup>

*Peer Reviewed By: James Lewis, Pharm.D., Infectious Diseases Clinical Coordinator, Oregon Health & Science University and Tracy Klein, PhD, FNP, Assistant Professor, College of Nursing, Washington State University Vancouver*

**References:**

1. Foxman B. Urinary tract infection syndromes: Occurrence, recurrence, bacteriology, risk factors, and disease burden. *Infect Dis Clin North Am.* 2014;28(1):1-13.
2. Hooton TM. Uncomplicated urinary tract infection. *N Engl J Med.* 2012;366(11):1028-1037.
3. Gupta K, Hooton 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. *Clinical Infectious Diseases.* 2011;52(5):e103-e120.
4. Shepherd AK, Pottinger PS. Management of urinary tract infections in the era of increasing antimicrobial resistance. *Med Clin North Am.* 2013;97(4):737-757.
5. Kallen AJ, Welch H, Sirovich BE. Current antibiotic therapy for isolated urinary tract infections in women. *Archives of Internal Medicine.* 2006;166(6):635-639.
6. Sandberg T, Skoog G, Hermansson AB, et al. Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: A randomised, open-label and double-blind, placebo-controlled, non-inferiority trial. *The Lancet.* 2012;380(9840):484-490.
7. Talan DA, Stamm WE, Hooton TM, et al. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis in women: A randomized trial. *JAMA.* 2000;283(12):1583-1590.
8. Eliakim-Raz N, Yahav D, Paul M, Leibovici L. Duration of antibiotic treatment for acute pyelonephritis and septic urinary tract infection— 7 days or less versus longer treatment: Systematic review and meta-analysis of randomized controlled trials. *Journal of Antimicrobial Chemotherapy.* 2013;68(10):2183-2191.
9. Lane DR, Takhar SS. Diagnosis and management of urinary tract infection and pyelonephritis. *Emerg Med Clin North Am.* 2011;29(3):539-552.
10. Gupta K, Hooton TM, Roberts PL, Stamm WE. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. *Archives of Internal Medicine.* 2007;167(20):2207-2212.
11. Grigoryan L, Trautner BW, Gupta K. Diagnosis and management of urinary tract infections in the outpatient setting: A review. *JAMA.* 2014;312(16):1677-1684.
12. Grabe M, Bartoletti R, Bjerklund-Johansen T, et al. Guidelines on urological infections. *European association of urology.* Updated March 2015. Available at <http://uroweb.org/guideline/urological-infections/>. Accessed 11 May 2015.
13. Shepherd AK, Pottinger PS. Management of urinary tract infections in the era of increasing antimicrobial resistance. *Med Clin North Am.* 2013;97(4):737-757.
14. OHSU adult outpatient antibiogram 2012. OHSU Department of Pharmacy services; 2012. OHSU Drug Information/Drug Policy Services and OHSU Clinical Microbiology Laboratories, ed.
15. Legacy health system adult outpatient antibiogram. ; 2011. Legacy Health System Microbiology Department, ed.
16. DRugs for urinary tract infections. *JAMA.* 2014;311(8):855-856.
17. Esposito S, Esposito I, Leone S. Considerations of antibiotic therapy duration in community- and hospital-acquired bacterial infections. *Journal of Antimicrobial Chemotherapy.* 2012;67(11):2570-2575.
18. Rice LB. The maxwell finland lecture: For the duration— rational antibiotic administration in an era of antimicrobial resistance and clostridium difficile. *Clinical Infectious Diseases.* 2008;46(4):491-496.
19. Drekonja DM, Okoye NC, Kuskowski MA, Johnson JR. Appropriateness of urinary tract infection diagnosis and treatment duration. *Archives of Internal Medicine.* 2010;170(5):489-490.

