RESEARCH ARTICLE

Update: Rational antibiotic treatment of outpatient genitourinary infections in a changing environment

Authors
Joshua A. Sherman, MD[a], Peter M.C. DeBlieux, MD[b]

Affiliations
[a]Advocate Christ Medical Center, Oak Lawn, Illionis, USA;
[b]Louisiana State University Health Sciences Center, University Medical Center, New Orleans, Louisiana, USA

Corresponding Author:
Peter M.C. DeBlieux
Email: peter.deblieux@lcmchealth.org

Abstract

Urinary tract infections (UTIs) are the most common bacterial infections presenting in the outpatient setting. Choosing the right empiric treatment for genitourinary infections continues to become more difficult due to increases in antimicrobial resistance, shifting and unpredictable regional resistance patterns, and changing etiologies. Even uncomplicated, community-acquired urinary tract infections generally considered easy to treat, are posing therapeutic challenges. UTIs are classified as uncomplicated or complicated. Uncomplicated UTIs occur in sexually active healthy female patients with structurally and functionally normal urinary tracts. Complicated UTIs are those that are associated with structural anatomic abnormalities or comorbid conditions that prolong the need for treatment, increasing the chances for therapeutic failure. All UTIs in male patients are considered complicated as are those that occur in the setting of pregnancy, chemotherapy and/or other immunosuppression. Escherichia coli is generally considered the most common cause of UTI--especially in uncomplicated, community-acquired infections – accounting for 75-95%. Alleviation of symptoms and prevention of complications are short-term treatment goals for UTIs. Long-term goals include prevention of recurrent infection and improvement in rate of reinfection. The Infectious Disease Society of America guidelines currently recommend Nitrofurantoin as first-line therapy for uncomplicated UTIs when local uropathogen resistance to TMP-SMX exceeds 20%, an increasingly common occurrence that underscores the need for clinicians to be aware of resistance patterns in their community. Alternatively, where available and cost-efficient, Fosfomycin or Pivmecillinam should be considered prior to alternative antimicrobial therapy in the form of either fluoroquinolones or beta-lactams. The best approach for treating outpatient UTIs focuses on adapting antimicrobial therapy to rapidly changing bacterial resistance patterns.

Choosing the right empiric treatment for genitourinary infections (GUIs) continues to become more difficult due to increases in antimicrobial resistance, shifting and unpredictable regional resistance patterns, and changing etiologies. Even uncomplicated, community-acquired urinary tract infections (UTIs), generally considered easy to treat, are posing therapeutic challenges.1 Here we offer an updated review of current treatment options for GUIs.

Epidemiology

In the United States, UTIs account for ~7-8 million office visits and 100,000 hospitalizations yearly, making them the most common bacterial infections in outpatient settings.[2,3] Approximately 1 in 3 women will require antimicrobial treatment for a UTI before age 24, and 40% to 50% of women will have a UTI during their lifetime.2 The estimated annual cost of UTIs is $1.6 billion for evaluation and treatment.3 Despite advances in antimicrobial therapy, UTIs remain a significant cause of morbidity.[2,4]

Table 1 Differential diagnosis of genitourinary infections (GUIs)

	GUI		
	Cystitis	Pyelonephritis	Prostatitis
Symptoms • Pyuria	• Dysuria	• Fever • Flank pain	• Low back pain • Dysuria • Prostate inflammation • Infection in prostatic fluid

Adapted from *Brazilian Journal of Urology*,[7] *Infect Dis Clin North Am*,[9] and *Sex Transm Infect.*[10]

Classification and diagnosis

UTIs are classified as uncomplicated or complicated. Uncomplicated UTIs occur in sexually active healthy female patients with structurally and functionally normal urinary tracts. Complicated UTIs are those that are associated with comorbid conditions that prolong the need for treatment or increase the chances for therapeutic failure. These conditions include abnormalities of the urinary tract that impede urine flow, the existence of a foreign body (e.g., indwelling catheter, stone), or infection with multidrug-resistant pathogens. All UTIs in male patients are considered complicated as are those that occur in the setting of pregnancy, chemotherapy and/or other immunosuppression[46]. Despite involvement of the upper urinary tract, pyelonephritis in women can be considered uncomplicated pyelonephritis when it occurs in a healthy patient.[5,6]

Women are significantly more susceptible than men to UTIs, although the pathogenic strains involved tend to be more virulent in men.[5] Sexually transmitted diseases (STDs) are considered the leading cause of GUIs in men aged < 50. Prostatitis is the most common urologic diagnosis in men >50 years of age, affecting about 50% of men during their lifetime.[7]

The diagnosis of a UTI largely relies on clinical symptoms and a limited number of laboratory findings (**Table 1**).[7,9,10] Prostate-specific antigen (PSA) levels may be elevated in both acute and chronic bacterial prostatitis. Men who present with an elevated PSA level and findings of prostatitis should be given a course of antibiotics followed by a repeat PSA measurement before a biopsy is performed.[11]

Risk factors

Because of the shorter length of their urethra, women, in general, are at greater risk than men of contracting UTIs. Other patients at increased risk of complications of UTIs include infants, pregnant women, and the elderly, as well as those with spinal cord injuries, indwelling catheters, diabetes mellitus, multiple sclerosis, human immunodeficiency virus or acquired immunodeficiency syndrome, underlying urologic abnormalities, or a prior history of UTI.[2]

Among premenopausal women, use of diaphragms, condoms, and/or spermicides for contraception are also risk factors for UTIs.[2,5] The most important risk factor for complicated UTI is obstruction.[5] Other factors associated with complicated UTIs or pyelonephritis include advanced age, diabetes, male sex, menopause, use of immunosuppressive drugs, and recent antibiotic use.[12]

Etiology

Escherichia coli is generally considered the most common cause of UTI--especially in uncomplicated, community-acquired infections – accounting for 75-95%. Recent evidence supports more substantial roles for other pathogens such as Staphylococcus Saprophyticus (accounting for 10-15% of UTIs) and other less commonly encountered pathogens including Proteus, Klebsiella and Escherichia faecalis[47]. Non–*E coli* pathogens play substantial etiologic roles in complicated UTIs; for instance, one study found that among spinal cord injury patients, 30% of acute UTIs were caused by *Klebsiella* species, 22% by *Enterococcus* species, and only 22% by *E coli*.[15] This shift in the etiology of UTIs should be taken into account when choosing empiric therapy.

Treatment goals

Alleviation of symptoms and prevention of complications are short-term treatment goals for UTIs.[16] Long-term goals include prevention of recurrent infection and improvement in rate of reinfection.[16] Since the morbidity of uncomplicated UTIs seems to be limited to the symptoms caused by the infection, the primary goal of treatment is symptom alleviation.[9,17] Convenience (including infrequent dosing intervals), safety, existing antibiotic resistance patterns, the generation of resistance, tolerability, and cost are considerations when choosing therapy.[9]

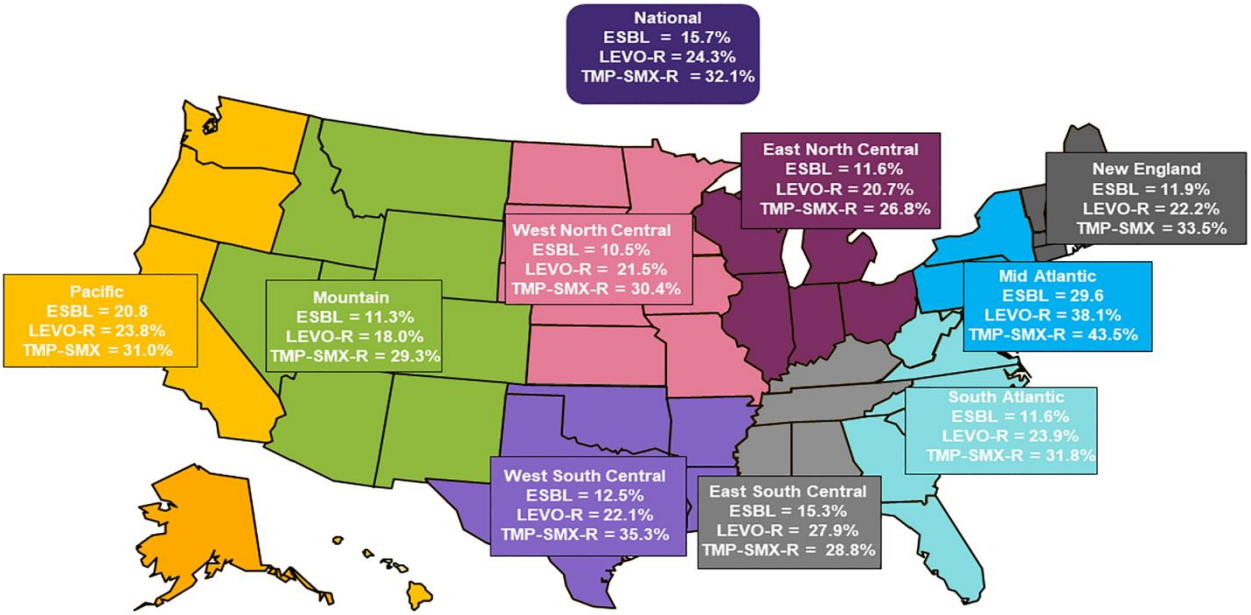


Figure 1: Photo credit: Fig National and regional prevalence of ESBL phenotypes, levofloxacin- and trimethoprim-sulfamethoxazole-resistant phenotypes of E. coli from UTIs in the USA in 2017.

Application of the Council for Appropriate and Rational Antibiotic Therapy criteria

Considering the changing etiology of UTIs as well as increasing antimicrobial resistance, a new paradigm is necessary to guide treatment choices. To aid in the selection of appropriate antimicrobial treatments for infectious diseases, the Council for Appropriate and Rational Antibiotic Therapy (CARAT) recommends determining whether a treatment choice is (1) supported by clinical evidence, (2) likely to provide therapeutic benefits, (3) safe, (4) the optimal drug for the optimal duration, and (5) cost-effective. The Council represents a multidisciplinary group of healthcare professionals established to advocate for the appropriate and accurate use of antimicrobials.

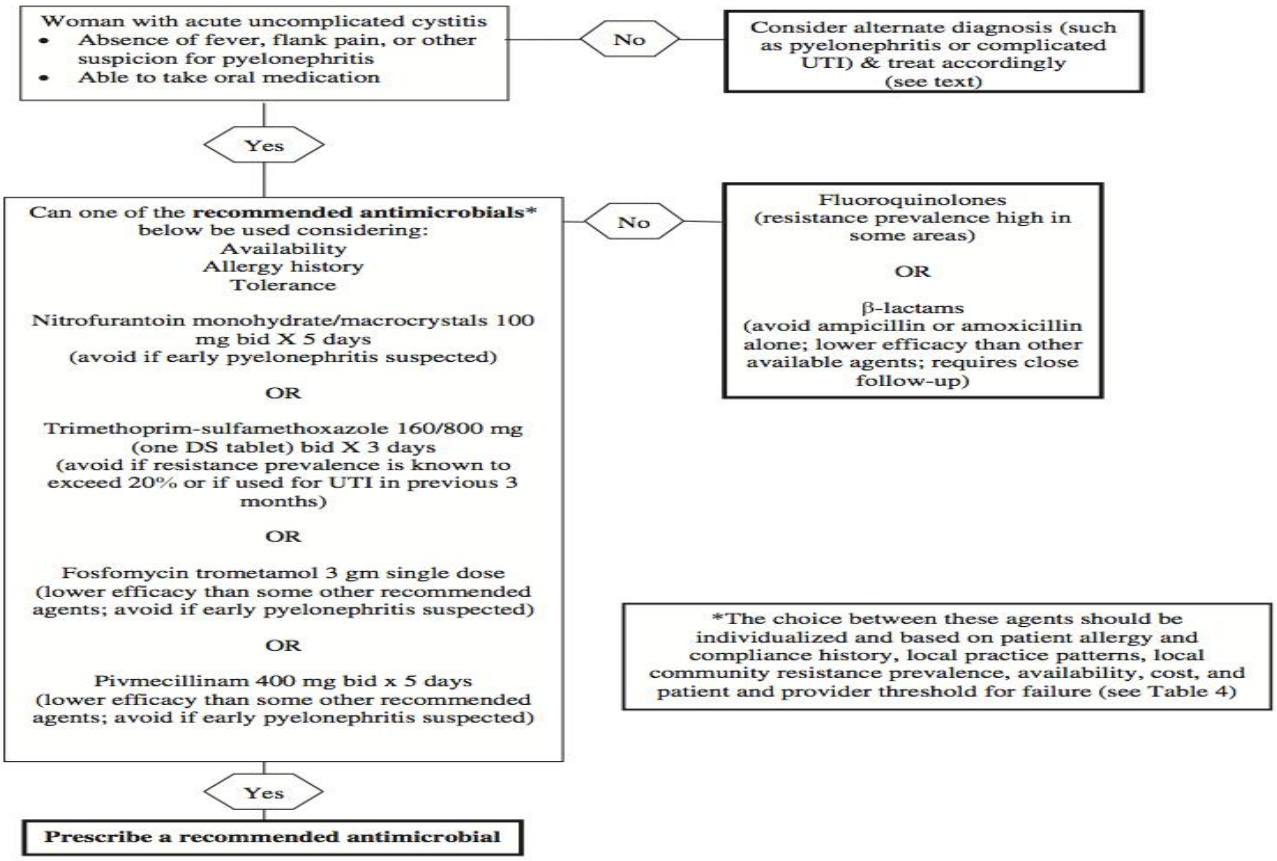
This article will discuss how these criteria can be applied to the treatment of UTIs in the outpatient setting.

Evidence-based therapy

UTIs

Evidence-based guidelines are available that have been formulated from clinical trial data. These guidelines provide useful resources for practicing clinicians. In the treatment of acute uncomplicated UTIs, for example, the 2019 Sanford Guide to Antimicrobial Therapy notes that resistance of E coli to trimethoprim-sulfamethoxazole (TMP-SMX) is high (15% to 20%) and correlates with microbiologic and clinical failure. Therefore, in areas where local resistance is <20%, TMP-SMX can be considered; in areas where local resistance is >20%, Nitrofurantoin should be given as first line. This is a significant change from the previous recommendations in which fluoroquinolones were considered first-line therapy.

The Infectious Diseases Society of America (IDSA) has proposed evidence-based guidelines for the management of UTIs.4 These guidelines, published in 2010, recommend the use of Nitrofurantoin for 5 days as standard of care (OR TMP-SMX for 3 days for uncomplicated bacterial cystitis, in regions where TMP- SMX resistance is below 20%). In recent years, resistance to TMP-SMX has increased relatively dramatically (Figure 1) while nitrofurantoin has continued to demonstrate minimal resistance and an efficacy comparable to 3 days of TMP-SMX. The 2010 IDSA guidelines go on to recommend several alternative agents to Nitrofurantoin and TMP-SMX (when indicated for cost, tolerance, resistance etc.) including the following: Fosfomycin trometamol 3g x 1 single dose (where available) and fluoroquinolones such as ofloxacin, ciprofloxacin and/or levofloxacin which are still relatively efficacious in 3-day regimens; however, there must be some consideration for these drugs' relative propensity for collateral damage (i.e. their potential adverse effects such as selection of drug-resistant organisms and colonization or infection with multidrug resistant organisms).44 It is generally recommended that fluoroquinolones be considered alternative therapy for acute cystitis and, instead, reserved for indications other than acute uncomplicated cystitis, when possible (FDA 2016; Gupta 2011).



Beta lactams such as amoxicillin-clavulanate and cefdinir are also considered appropriate therapy when other agents cannot be used. These should also be used with caution due to an increased side effect profile and relatively lower efficacy when compared to other antimicrobials used for treatment of acute cystitis. It is worth noting that although cephalexin is not formally recommended by the IDSA for the treatment of uncomplicated UTI, it is commonly used in the outpatient setting and generally considered acceptable (Gupta 2011).

Figure 2, adapted from *IDSociety.org*, offers a summary of the 2010 IDSA guidelines for the treatment of acute uncomplicated cystitis.

Pyelonephritis and prostatitis

The 2019 *Sanford Guide to Antimicrobial Therapy* continues to recommend a fluoroquinolone as first-line therapy for acute uncomplicated pyelonephritis.[18] For acute prostatitis in men <35 years of age, ceftriaxone followed by doxycycline is recommended if there is clinical or historical concern for an STI. Alternatively, if this concern is not present, TMP-SMX or an oral fluoroquinolone is the recommended empiric therapy. In men aged >35 years, fluoroquinolones or TMP-SMX are recommended.[18]

Recommendations for the treatment of acute pyelonephritis and acute bacterial prostatitis from the IDSA and Sanford Guide are summarized on Table 2. Note that in order to be effective for the treatment of bacterial prostatitis, an antibiotic must be able to attain sufficient concentrations in the prostatic fluid to achieve bactericidal levels. Only trimethoprim and the fluoroquinolones possess both the appropriate bactericidal activity and the ability to diffuse into the prostate.[24] For example, ciprofloxacin attains a prostatic tissue-to-serum ratio of 1.86:1.25 Levofloxacin shows particularly good penetration into prostatic tissue, attaining a prostatic tissue-to-serum ratio of 2.96:1.[26] A few special considerations are worthy

of mention when interpreting Table 2 as it relates to the various treatment options for acute pyelonephritis: [1]If local resistance to fluroquinolones is known to be >10%, the IDSA recommends an initial dose of Ceftriaxone or an aminoglycoside such as gentamicin at the initiation of therapy. The same recommendation stands when oral beta-lactams or TMP-SMX are used in place of fluoroquinolones as the former tend to be generally less effective and have shown higher replace rates in previous studies (Gupta 2011)[3] while the latter are often considered sub-optimal as first line, especially in scenarios where local and/or personal resistance is unknown[2].

Table 2

Acute Uncomplicated Pyelonephritis Rx:		
Cip rofloxacin[1]	500mg PO BID	7 days
Levofloxacin[1]	750mg PO daily	5 days
TMP-SMX[2]	160/800mg PO BID	14 days
Cefpodoxime [3]	200mg PO BID	10-14 days
Amox-Clav[3]	500mg TID	10-14 days

Lastly, note that Fosfomycin and nitrofurantoin, while usually effective for the treatment of acute cystitis, are not effective treatment options for pyelonephritis given that both are mainly concentrated in the bladder and fail to adequately penetrate the renal parenchyma[45].

Therapeutic benefits

To stem future increases in resistance, clinicians must use their hospital-generated antibiogram to choose the antibiotic most likely to eradicate the infection as the first line of treatment. Treatment failure not only costs more money, it also drives future resistance.[27] Therefore, it is critical for clinicians to know their own local resistance patterns and prescribe accordingly. Outpatient data on antimicrobial resistance patterns is particularly beneficial in assisting Providers with evidenced based decisions. It has been found that despite increasing resistance to some commonly used antimicrobials, many clinicians do not consider antimicrobial resistance a problem in their own institution or practice.[28]

It has been demonstrated in prospective clinical trials that in vitro susceptibility data correlate with in vivo treatment results. Based upon the correlation between resistance and treatment failure, clinicians should consider local resistance patterns carefully when choosing an antibiotic treatment for a UTI.

(Acute) Bacterial Prostatitis:

</= 35, concern for STI	IM Ceftriaxone followed by Doxycycline	
Uncomplicated, low risk for STI	Levofloxacin 500-750mg PO Daily Ofloxacin 300mg PO BID TMP-SMX 160/800mg PO BID	All with 10-14-day minimum therapy with some experts advocating for 4 weeks duration.

UTIs

E coli resistance to beta-lactams and first-generation cephalosporins has increased steadily over the last several decades[1]. One of the most notable and alarming shifts have occurred in resistance to TMP-SMX, one of the principal recommended treatments for uncomplicated UTIs.[4] Indeed, nationwide, *E coli* resistance to TMP-SMX is now >20% in the United States[30] and displays geographic variation (Figure 1).[31] In fact, 7.1% of *E coli* strains have shown multidrug resistance to >3 antimicrobials, such as combinations of ampicillin, cephalothin, ciprofloxacin and TMP-SMX.[32] These multidrug-resistant *E coli* isolates were most resistant to TMP-SMX, ampicillin, or cephalothin (>80%) as individual agents and least resistant to nitrofurantoin (7.7%). The most common multidrug-resistant phenotype (57.9%) was resistant to TMP-SMX, ampicillin, and cephalothin.[32]

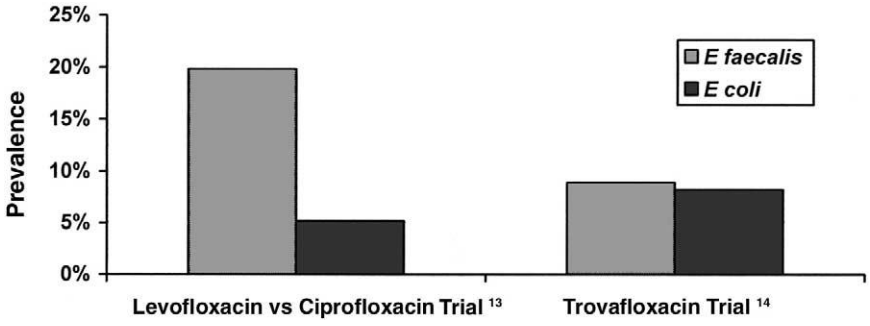


Figure 2 Prevalence of Enterococcus faecalis versus Escherichia coli in 2 recent clinical trials. (Adapted from Urology13 and Trovan (trovafloxacin) New Drug Application.14

Table 3:

Council for Appropriate and Rational Antibiotic Therapy Criteria:
• Evidence-Based results
• Therapeutic Benefits
• Safety
• Cost-Effectiveness
• Optimal drug dose & duration

Although E coli is traditionally considered the most common cause of UTIs, investigators have recently highlighted the polymicrobial nature of acute UTIs in some patient groups. For example, in patients with spinal cord injury, one third of infections were polymicrobial, some- times with a mix of gram-negative as well as gram-positive strains (chiefly Enterococcus species).15 Thus, to optimize the therapeutic benefits of antimicrobial therapy in uncomplicated UTIs, the aforementioned CARAT criteria (Table 3) should then support the use of broad-spectrum antibiotics active against both gram-negative and gram-positive strains. It is speculated that the increase in gram-positive pathogens may be due to the previous widespread use of ciprofloxacin for treating UTIs.34,35 Levofloxacin and gatifloxacin offer coverage for both the gram-negative and gram-positive pathogens, making these agents preferable in treating UTIs empirically in such patient groups.

Safety

The safety and tolerability of antimicrobial treatments vary widely. Even among the fluoroquinolones -- which are generally considered safe and effective -- some safety issues warrant review. These issues, including damage to normal intestinal flora and Clostridium difficile–associated diarrhea, can be found in various publications exploring this very topic. This concern, as well as other rare but potentially serious side effects of fluoroquinolones, prompted an FDA black box warning in 2008.

Optimal drug for optimal duration

The goal of choosing the optimal drug for the optimal duration is to provide the most targeted, effective therapy that will achieve clinical efficacy while preventing or minimizing increases in resistance. Short-course therapy is generally considered the preferred treatment for uncomplicated UTIs.[16,17] Short courses of therapy enhance tolerability and adherence, and also reduce cost without decreasing efficacy.[17] Short-course therapy may help prevent selection for resistant organisms.

Preventing increases in resistance

In the treatment of UTIs, the application of the CARAT criteria can optimize outcomes and may slow the spread of resistant bacterial strains. A principal goal of the CARAT criteria is to encourage the use of the optimal antimicrobial for the optimal duration, or the use of the most bacteriologically and clinically efficacious agent for the shortest time necessary to achieve clinical success and to prevent the increases in antimicrobial resistance that have been associated with treatment failure in UTIs.[29] In the management of uncomplicated GUIs, antimicrobials with a broad spectrum of activity may sometimes provide the optimal treatment advocated by the CARAT criteria, because these agents offer the greatest opportunity for averting the spread of resistant organisms and treatment failure.

Cost

The true cost-effectiveness of an antimicrobial treatment is determined by many variables.

Treatment failures result in increased costs that may be due to a variety of factors, including antibiotic resistance or poor adherence. Factors that influence adherence to therapy include dose frequency and length of treatment, as well as side-effect profile and frequency.[37] Because less frequent dosing has been associated with enhanced adherence, shorter courses of therapy with a reduced pill burden should address this problem in addition to reducing the risk of some adverse events.[38,39]

The available treatment options offer different dosing regimens for each indication. Due to the influence of pill burden on adherence, the total pill burden should be considered for each treatment option.

Summary

The CARAT criteria provide a sound approach for adapting antimicrobial therapy to rapidly changing bacterial resistance patterns. These criteria imply that optimal antimicrobial treatment for GUIs can be achieved with antimicrobials that provide effective, well-tolerated, convenient treatment that can bolster adherence, possibly decreasing the need for retreatment and reducing the potential for resistance. The IDSA guidelines recommend Nitrofurantoin as first-line therapy for uncomplicated UTIs when local uropathogen resistance to TMP-SMX exceeds 20%, an increasingly common occurrence that underscores the need for clinicians to be aware of resistance patterns in their community. Alternatively, where available and cost-efficient, Fosfomycin or Pivmecillinam should be considered prior to alternative antimicrobial therapy in the form of either fluoroquinolones or beta-lactams.

References

1. Gupta K, Hooton TM, Stamm WE. Increasing antimicrobial resistance and the management of uncomplicated community-acquired urinary tract infections. *Ann Intern Med.* 2001;135:41–50.
2. Foxman B. Epidemiology of urinary tract infections: incidence, mor- bidity, and economic costs. *Am J Med.* 2002;113(suppl):5S–13S.
3. Foxman B. Epidemiology of urinary tract infections: incidence, mor- bidity, and economic costs. *Dis Mon.* 2003;49:53–70.
4. Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. *Clin Infect Dis.* 1999;29:745–758.
5. Hooton TM. Pathogenesis of urinary tract infections: an update. *J Antimicrob Chemother.* 2000;46:1–7.
6. Stapleton AE. Urinary tract infections in healthy women. *Curr Treat Opt Infect Dis.* 2003;5:43–51.
7. Schaeffer AJ. Diagnosis and management of prostatitis. *Brazilian Journal of Urology* 2000;26:122–131.
8. Nicolle LE. Epidemiology of urinary tract infection. *Infect Med.* 2001; 18:153–162.
9. Hooton TM, Stamm WE. Diagnosis and treatment of uncomplicated urinary tract infection. *Infect Dis Clin North Am.* 1997;11:551–581.
10. Clinical Effectiveness Group (Association of Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases). National guideline for the management of prostatitis. *Sex Transm Infect.* 1999; 75(suppl 1):S46 –S50.
11. Jack GS, Zeitlin SI. Confronting prostatitis: is your management strat- egy up-to-date? *Contemp Urol.* 2004;16:34 – 46.
12. McCue J. UTIs in at-risk patients: are they complicated? *Infect Med.* 1999;16:533–540.
13. Bundrick W, Heron SP, Ray P, et al. Levofloxacin versus ciprofloxacin in the treatment of chronic bacterial prostatitis: a randomized double- blind multicenter study. *Urology.* 2003;62:537–541.
14. Trovan® (trovafloxacin) New Drug Application. US Food and Drug Administration Web site. Available at: http://www.fda.gov/cder/foi/ nda/97/020760a_medr_P6.pdf. Accessed October 13, 2004.
15. Dow G, Rao P, Harding G, et al. A prospective, randomized trial of 3 of 14 days of ciprofloxacin treatment for acute urinary tract infection in patients with spinal cord injury. *Clin Infect Dis.* 2004;39:658 – 664.
16. Nicolle L. Best pharmacological practice: urinary tract infections. *Expert Opin Pharmacother.* 2003;4:693–704.
17. Naber KG. Short-term therapy of acute uncomplicated cystitis. *Curr Opin Urol.* 1999;9:57– 64.
18. Gilbert DN, Moellering RC Jr, Eliopoulos GM, Sande MA. *The San- ford Guide to Antimicrobial Therapy*, 34th ed. Hyde Park, VT: Anti- microbial Therapy, Inc., 2004.
19. Data on file. The Surveillance Network (TSN) Database 2003. Raritan, NJ: Ortho-McNeil Pharmaceutical, Inc., 2003.
20. Stamm WE, Norrby SR. Urinary tract infections: disease panorama and challenges. *J Infect Dis* 2001;183(suppl 1):S1–S4.
21. Nicolle LE. Urinary tract infection: traditional pharmacologic thera- pies. *Am J Med* 2002;113(suppl 1A):35S– 44S.
22. Gupta K, Sahm DF, Mayfield D, Stamm WE. Antimicrobial resistance among uropathogens that cause community-acquired urinary tract in- fections in women: a nationwide analysis. *Clin Infect Dis.* 2001;33: 89 –94.
23. Lummus WE, Thompson I. Prostatitis. *Emerg Med Clin North Am.* 2001;19:691–707.
24. Fowler JE Jr. Antimicrobial therapy for bacterial and nonbacterial prostatitis. *Urology.* 2002;60:24 –26.
25. Zhanel GG, Ennis K, Vercaigne L, et al. A

critical review of the fluoroquinolones: focus on respiratory infections. *Drugs.* 2002;62:13–59.
26. Drusano GL, Preston SL, Van Guilder M, et al. A population phar- macokinetic analysis of the penetration of the prostate by levofloxacin. *Antimicrob Agents Chemother.* 2000;44:2046–2051.
27. Nicolau D. Clinical and economic implications of antimicrobial resis- tance for the management of community-acquired respiratory tract infections. *J Antimicrob Chemother* 2002;50(suppl S1):61–70.
28. Giblin TB, Sinkowitz-Cochran RL, Harris PL, et al, for the CDC Campaign to Prevent Antimicrobial Resistance Team. Clinicians' per- ceptions of the problem of antimicrobial resistance in health care facilities. *Arch Intern Med.* 2004;164:1662–1668.
29. Talan DA, Stamm WE, Hooton TM, et al. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute un- complicated pyelonephritis in women: a randomized trial. *JAMA.* 2000;283:1583–1590.
30. Data on file. Proceedings of the TRUST 8 (2004) Investigators' Meet- ing; May 25, 2004; New Orleans, LA. Raritan, NJ: Ortho-McNeil Pharmaceutical, Inc., 2004.
31. Data on file. Proceedings of the TRUST 7 (2002-2003) Surveillance Study. Raritan, NJ: Ortho-McNeil Pharmaceutical, Inc., 2003.
32. Sahm DF, Thornsberry C, Mayfield DC, Jones ME, Karlowsky JA. Multidrug-resistant urinary tract isolates of *Escherichia coli*: preva- lence and patient demographics in the United States in 2000. *Antimi- crob Agents Chemother.* 2001;45:1402–1406.
33. Hepburn MJ, Dooley DP, Skidmore PJ, Ellis MW, Starnes WF, Hasewinkle WC. Comparison of short-course (5 days) and standard (10 days) treatment for uncomplicated cellulitis. *Arch Intern Med.* 2004;164:1669–1674.
34. Zhanel GG, Walters M, Laing N, Hoban DJ. *In vitro* pharmacody- namic modelling simulating free serum concentrations of fluoroquino- lones against multidrug-resistant *Streptococcus pneumoniae*. *J Antimi- crob Chemother.* 2001;47:435–440.
35. Klepser ME, Ernst EJ, Petzold CR, Rhomberg P, Doern GV. Comparative bactericidal activities of ciprofloxacin, clinafloxacin, grepafloxacin, levo- floxacin, moxifloxacin, and trovafloxacin against *Streptococcus pneu- moniae* in a dynamic in vitro model. *Antimicrob Agents Chemother.* 2001;45:673–678.
36. Liu H, Mulholland SG. Appropriate antibiotic treatment of genitouri- nary infections in hospitalized patients. *Am J Med.* 2005;118(suppl 7A):14S–20S.
37. Kardas P. Patient compliance with antibiotic treatment for respiratory tract infections. *J Antimicrob Chemother.* 2002;49:897–903
38. File TM Jr. Clinical efficacy of newer agents in short-duration therapy for community-acquired pneumonia. *Clin Infect Dis.* 2004;39(suppl 3):S159–S164.
39. Claxton AJ, Cramer J, Pierce C. A systematic review of the associa- tions between dose regimens and medication compliance. *Clin Ther.* 2001;23:1296–1310.
40. Levaquin [package insert]. Raritan, NJ: Ortho-McNeil Pharmaceutical, Inc.; 2004.
41. Cipro [package insert]. West Haven, CT: Bayer Pharmaceuticals Cor- poration; 2004.
42. Tequin [package insert]. Princeton, NJ: Bristol-Myers Squibb Com- pany; 2004.
43. Critchley IA, Cotroneo N, Pucci MJ, Mendes R (2019) The burden of antimicrobial resistance among urinary tract isolates of *Escherichia coli* in the United States in 2017. PLOS ONE 14(12): e0220265.
44. Paterson DL. "Collateral damage" from cephalosporin and quinolone antibiotic therapy. Clin Infect Dis 2004; 38(Suppl. 4):S341-5.
45. 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 Disease Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;5:e103-20
46. Long B., and Koyfman .: The emergency

department diagnosis and treatment of UTI. Emerg Med Clin North Am 2018; 36:pp 685-710

47. Ronald A.: The etiology of urinary tract infection: traditional and emerging pathogens. Am J Med 2002; 113:pp. 14S-19S

