

# Executive Summary: 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

Kalpana Gupta,<sup>1</sup> Thomas M. Hooton,<sup>2</sup> Kurt G. Naber,<sup>9</sup> Björn Wullt,<sup>10</sup> Richard Colgan,<sup>3</sup> Loren G. Miller,<sup>4</sup> Gregory J. Moran,<sup>5</sup> Lindsay E. Nicolle,<sup>8</sup> Raul Raz,<sup>11</sup> Anthony J. Schaeffer,<sup>6</sup> and David E. Soper<sup>7</sup>

<sup>1</sup>Department of Medicine, Veterans Affairs Boston Health Care System and Boston University School of Medicine, Boston, Massachusetts; <sup>2</sup>Department of Medicine, University of Miami Miller School of Medicine, University of Miami, Miami Florida; <sup>3</sup>Department of Family and Community Medicine, University of Maryland, Baltimore, Maryland; <sup>4</sup>Division of Infectious Diseases, Harbor-UCLA Medical Center, Torrance, and <sup>5</sup>Department of Emergency Medicine and Division of Infectious Diseases Olive View-UCLA Medical Center, Sylmar, California; <sup>6</sup> Department of urology, Northwestern University, Chicago, Illinois; and <sup>7</sup>Departments of Obstetrics and Gynecology and Medicine, Medical University of South Carolina, Charleston, South Carolina; <sup>8</sup>Department of Internal Medicine and Department of Medical Microbiology University of Manitoba, Winnipeg, Canada; <sup>9</sup>Technical University of Munich, Munich, Germany; <sup>10</sup>Lund University Hospital, Lund, Sweden; and <sup>11</sup>Infectious Diseases Unit, Ha'Emek Medical Center, Afula, and Rappaport Faculty of Medicine, Technion, Haifa, Israel

A Panel of International Experts was convened by the Infectious Diseases Society of America (IDSA) in collaboration with the European Society for Microbiology and Infectious Diseases (ESCMID) to update the 1999 Uncomplicated Urinary Tract Infection Guidelines by the IDSA. Co-sponsoring organizations include the American Congress of Obstetricians and Gynecologists, American Urological Association, Association of Medical Microbiology and Infectious Diseases–Canada, and the Society for Academic Emergency Medicine. The focus of this work is treatment of women with acute uncomplicated cystitis and pyelonephritis, diagnoses limited in these guidelines to premenopausal, non-pregnant women with no known urological abnormalities or co-morbidities. The issues of in vitro resistance prevalence and the ecological adverse effects of antimicrobial therapy (collateral damage) were considered as important factors in making optimal treatment choices and thus are reflected in the rankings of recommendations.

## EXECUTIVE SUMMARY

### BACKGROUND

Acute uncomplicated cystitis remains one of the most common indications for prescribing of antimicrobials to otherwise healthy community-dwelling women. Despite published guidelines for the optimal selection of an antimicrobial agent and duration of therapy, studies demonstrate a wide variation in prescribing practices [1–6]. The Infectious Diseases Society of America (IDSA) published a clinical practice guideline on the treatment of women with acute uncomplicated cystitis and pyelonephritis in 1999 [1]. Since then, antimicrobial resistance among uropathogens causing uncomplicated cystitis has increased, appreciation of the importance of

Received 10 December 2010; accepted 17 December 2010.

The process for evaluating the evidence was based on the IDSA Handbook on Clinical Practice Guideline Development and involved a systematic weighting of the quality of the evidence and the grade of recommendation (Table 1) [31].

It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The IDSA considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

Correspondence: Kalpana Gupta, MD, VA Boston HCS, 1400 VFW Pkwy, 111 Med, West Roxbury, MA 02132 (kalpana.gupta@va.gov).

**Clinical Infectious Diseases** 2011;52(5):561–564

© The Author 2011. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com  
1058-4838/2011/525-0001\$37.00

DOI: 10.1093/cid/cir102

**Table 1. Strength of Recommendations and Quality of Evidence**

Category/grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for or against use
B	Moderate evidence to support a recommendation for or against use
C	Poor evidence to support a recommendation
Quality of evidence	
I	Evidence from $\geq 1$ properly randomized, controlled trial
II	Evidence from $\geq 1$ well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from $>1$ center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

**NOTE.** Data are from the periodic health examination. Canadian Task Force on the Periodic Health Examination. Health Canada, 1979. Adapted and Reproduced with the permission of the Minister of Public Works and Government Services Canada, 2009 [31].

the ecological adverse effects of antimicrobial therapy (collateral damage) has increased, newer agents and different durations of therapy have been studied, and clinical outcomes have increasingly been reported. In addition, women with uropathogens resistant to the treatment drug have been included in some studies, allowing for estimations of expected response rates in a “real-life” clinical setting in which empirical therapy is prescribed either without a urine culture and susceptibility testing or before such results are known. In light of these developments, an update of the guidelines was warranted.

The focus of this guideline is treatment of women with acute uncomplicated cystitis and pyelonephritis, diagnoses limited in these guidelines to premenopausal, nonpregnant women with no known urological abnormalities or comorbidities. It should be noted that women who are postmenopausal or have well-controlled diabetes without urological sequelae may be considered by some experts to have uncomplicated urinary tract infection (UTI), but a discussion of specific management of these groups is outside the scope of this guideline. In addition, management of recurrent cystitis and of UTI in pregnant women, prevention of UTI, and diagnosis of UTI are all important issues that are not addressed in this guideline. The issues of in vitro resistance prevalence and the potential for collateral damage were considered as important factors in making optimal treatment choices and thus are reflected in the rankings of recommendations.

Summarized below are the recommendations made in the 2010 guideline update. The Panel followed a process used in the development of other IDSA guidelines which included a systematic weighting of the quality of the evidence and the grade of recommendation [32] (Table 1). A detailed description of the methods, background, and evidence summaries that support each of the recommendations can be found in the full text of the guideline.

### **I. What Is the Optimal Treatment for Acute Uncomplicated Cystitis?**

#### **Recommendations (Figure 1).**

1. Nitrofurantoin monohydrate/macrocrystals (100 mg twice daily for 5 days) is an appropriate choice for therapy due to minimal resistance and propensity for collateral damage (defined above) and efficacy comparable to 3 days of trimethoprim-sulfamethoxazole (A-I).

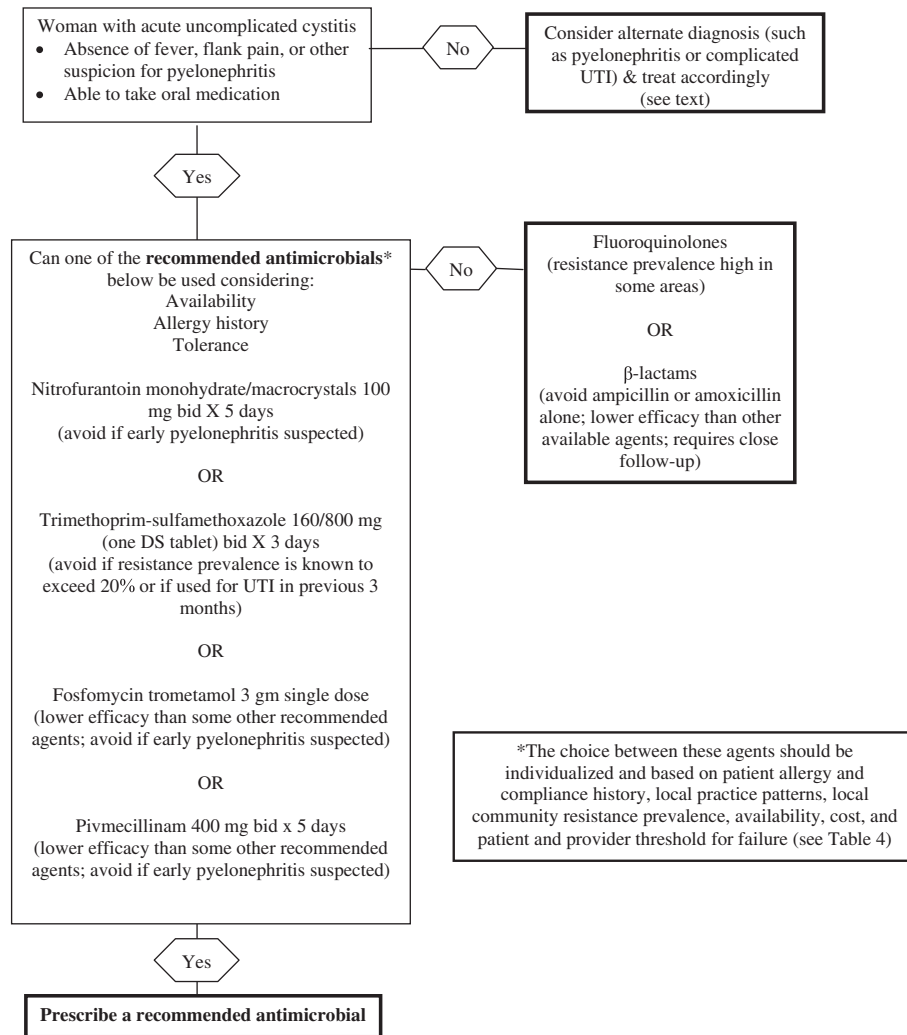
2. Trimethoprim-sulfamethoxazole (160/800 mg [1 double-strength tablet] twice-daily for 3 days) is an appropriate choice for therapy, given its efficacy as assessed in numerous clinical trials, if local resistance rates of uropathogens causing acute uncomplicated cystitis do not exceed 20% or if the infecting strain is known to be susceptible (A-I).

i. The threshold of 20% as the resistance prevalence at which the agent is no longer recommended for empirical treatment of acute cystitis is based on expert opinion derived from clinical, in vitro, and mathematical modeling studies (B-III).

ii. In some countries and regions, trimethoprim (100 mg twice daily for 3 days) is the preferred agent and is considered equivalent to trimethoprim-sulfamethoxazole on the basis of data presented in the original guideline (A-III) [1].

ii. Data are insufficient to make a recommendation for other cystitis antimicrobials as to what resistance prevalence should be used to preclude their use for empirical treatment of acute cystitis.

3. Fosfomycin trometamol (3 g in a single dose) is an appropriate choice for therapy where it is available due to minimal resistance and propensity for collateral damage, but it appears to have inferior efficacy compared with standard short-course regimens according to data submitted to the US Food and Drug Administration (FDA) and summarized in the Medical Letter (A-I) [7].



**Figure 1.** Approach to choosing an optimal antimicrobial agent for empirical treatment of acute uncomplicated cystitis. DS, double-strength; UTI, urinary tract infection.

4. Pivmecillinam (400 mg bid for 3–7 days) is an appropriate choice for therapy in regions where it is available (availability limited to some European countries; not licensed and/or available for use in North America), because of minimal resistance and propensity for collateral damage, but it may have inferior efficacy compared with other available therapies (A-I).

5. The fluoroquinolones, ofloxacin, ciprofloxacin, and levofloxacin, are highly efficacious in 3-day regimens (A-I) but have a propensity for collateral damage and should be reserved for important uses other than acute cystitis and thus should be considered alternative antimicrobials for acute cystitis (A-III).

6.  $\beta$ -Lactam agents, including amoxicillin-clavulanate, cefdinir, cefaclor, and cefpodoxime-proxetil, in 3–7-day regimens are appropriate choices for therapy when other recommended agents cannot be used (B - I). Other  $\beta$ -lactams, such as cephalexin, are less well studied but may also be appropriate in certain settings (B-III). The  $\beta$ -lactams generally have inferior efficacy and more adverse

effects, compared with other UTI antimicrobials (B-I). For these reasons,  $\beta$ -lactams other than pivmecillinam should be used with caution for uncomplicated cystitis.

7. Amoxicillin or ampicillin should not be used for empirical treatment given the relatively poor efficacy, as discussed in the 1999 guidelines [1] and the very high prevalence of antimicrobial resistance to these agents worldwide [8–11] (A-III).

## II. What Is the Treatment for Acute Pyelonephritis?

### Recommendations

8. In patients suspected of having pyelonephritis, a urine culture and susceptibility test should always be performed, and initial empirical therapy should be tailored appropriately on the basis of the infecting uropathogen (A-III).

9. Oral ciprofloxacin (500 mg twice daily) for 7 days, with or without an initial 400-mg dose of intravenous ciprofloxacin, is an

appropriate choice for therapy in patients not requiring hospitalization where the prevalence of resistance of community uropathogens to fluoroquinolones is not known to exceed 10% (A-I). If an initial one-time intravenous agent is used, a long-acting antimicrobial, such as 1 g of ceftriaxone or a consolidated 24-h dose of an aminoglycoside, could be used in lieu of an intravenous fluoroquinolone (B-III). If the prevalence of fluoroquinolone resistance is thought to exceed 10%, an initial 1-time intravenous dose of a long-acting parenteral antimicrobial, such as 1 g of ceftriaxone (B-III) or a consolidated 24-h dose of an aminoglycoside, is recommended (B-III).

i. Data are insufficient to make a recommendation about what fluoroquinolone resistance level requires an alternative agent in conjunction with or to replace a fluoroquinolone for treatment of pyelonephritis.

10. A once-daily oral fluoroquinolone, including ciprofloxacin (1000 mg extended release for 7 days) or levofloxacin (750 mg for 5 days), is an appropriate choice for therapy in patients not requiring hospitalization where the prevalence of resistance of community uropathogens is not known to exceed 10% (B-II). If the prevalence of fluoroquinolone resistance is thought to exceed 10%, an initial intravenous dose of a long-acting parenteral antimicrobial, such as 1 g of ceftriaxone (B-III) or a consolidated 24-h dose of an aminoglycoside, is recommended (B-III).

11. Oral trimethoprim-sulfamethoxazole (160/800 mg [1 double-strength tablet] twice-daily for 14 days) is an appropriate choice for therapy if the uropathogen is known to be susceptible (A-I). If trimethoprim-sulfamethoxazole is used when the susceptibility is not known, an initial intravenous dose of a long-acting parenteral antimicrobial, such as 1 g of ceftriaxone (B-II) or a consolidated 24-h dose of an aminoglycoside, is recommended (B-III).

12. Oral  $\beta$ -lactam agents are less effective than other available agents for treatment of pyelonephritis (B-III). If an oral  $\beta$ -lactam agent is used, an initial intravenous dose of a long-acting parenteral antimicrobial, such as 1 g of ceftriaxone (B-II) or a consolidated 24-h dose of an aminoglycoside, is recommended (B-III).

i. Data are insufficient to modify the previous guideline recommendation for a duration of therapy of 10–14 days for treatment of pyelonephritis with a  $\beta$ -lactam agent.

13. Women with pyelonephritis requiring hospitalization should be initially treated with an intravenous antimicrobial regimen, such as a fluoroquinolone; an aminoglycoside, with or without ampicillin; an extended-spectrum cephalosporin or extended-spectrum penicillin, with or without an aminoglycoside; or a carbapenem. The choice between these agents should be based on local resistance data, and the regimen should be tailored on the basis of susceptibility results (B-III).

## Acknowledgments

The Expert Panel dedicates this guideline to the memory of Dr. Walter E. Stamm, whose work and commitment over several decades enhanced our understanding of the pathogenesis, epidemiology, and management of urinary tract infections in women. We honor him as a colleague, mentor, and leader.

The Expert Panel wishes to express its gratitude to the IDSA staff for administrative assistance and external reviewers Drs Patricia Brown, Jack Sobel, and John Warren for thoughtful advice.

**Financial support.** The Infectious Diseases Society of America.

**Potential conflicts of interest.** K.G. (Chair) has served as a consultant to Pfizer and Pinnacle Pharmaceutical.A.J.S. has served as a consultant to Novabay Pharmaceuticals, Pfizer, Propagate Pharmaceuticals, Hagen/Sinclair Research Recruiting, Swiss Precision Diagnostics Development Company, and FlashPointMedica; has received honoraria from BMJ Group (British Medical Journal) and Advanstar Communications; received a royalty payment from UpToDate; and received remuneration from the American Urological Association. G.J.M. has served as a consultant to Cerexa, Cubist, Eisai, Forest, Merck, Ortho-McNeil, Pfizer, and Schering-Plough and has received honoraria from Cubist and Merck. K.G.N. has received remuneration as consultant or speaker from Bionorica, Daiichi Sankyo, Janssen Cilag, Johnson & Johnson, OM Pharma, Pierre Fabre, Sanofi Aventis, and Zambon and has received research grants from MerLion Pharmaceuticals, Rosen Pharma, and OM Pharma.L.E.N. has served as a consultant to Pfizer, Leo pharmaceuticals, Cerexa, and Johnson & Johnson and served on the advisory board for Leo Pharmaceuticals and Cerexa.L.G.M. has served as a consultant to Forest and Theravance Laboratories and received research grants from Cubist and Pfizer Pharmaceuticals. T.M.H. has served as a consultant to Pfizer, Alita Pharmaceuticals, and Pinnacle Pharmaceuticals. All other authors: no conflicts.

## References

- 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. Infectious Diseases Society of America (IDSA). *Clin Infect Dis* **1999**; 29:745–58.
- Huang ES, Stafford RS. National patterns in the treatment of urinary tract infections in women by ambulatory care physicians. *Archives of internal medicine* **2002**; 162:41–7.
- Kahan NR, Chinitz DP, Kahan E. Longer than recommended empiric antibiotic treatment of urinary tract infection in women: an avoidable waste of money. *Journal of clinical pharmacy and therapeutics* **2004**; 29:59–63.
- Kallen AJ, Welch HG, Sirovich BE. Current antibiotic therapy for isolated urinary tract infections in women. *Archives of internal medicine* **2006**; 166:635–9.
- O'Connor PJ, Solberg LI, Christianson J, Amundson G, Mosser G. Mechanism of action and impact of a cystitis clinical practice guideline on outcomes and costs of care in an HMO. *The Joint Commission journal on quality improvement* **1996**; 22:673–82.
- Stamm WE. Evaluating guidelines. *Clin Infect Dis* **2007**; 44:775–6.
- Fosfomycin for urinary tract infections. *Med Lett Drugs Ther* **1997**; 39:66–8. PMID: 9255237.
- Kahlmeter G. An international survey of the antimicrobial susceptibility of pathogens from uncomplicated urinary tract infections: the ECO.SENS Project. *J Antimicrob Chemother* **2003**; 51:69–76.
- Kahlmeter G. Prevalence and antimicrobial susceptibility of pathogens in uncomplicated cystitis in Europe. The ECO.SENS study. *Int J Antimicrob Agents* **2003**; 22(Suppl. 2):49–52.
- Naber KG, Schito G, Botto H, Palou J, Mazzei T. Surveillance study in Europe and Brazil on clinical aspects and Antimicrobial Resistance Epidemiology in Females with Cystitis (ARESC): implications for empiric therapy. *Eur Urol* **2008**; 54:1164–75.
- Zhanell GG, Hisanaga TL, Laing NM, et al. Antibiotic resistance in *Escherichia coli* outpatient urinary isolates: final results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA). *Int J Antimicrob Agents* **2006**; 27:468–75.