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

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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

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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.

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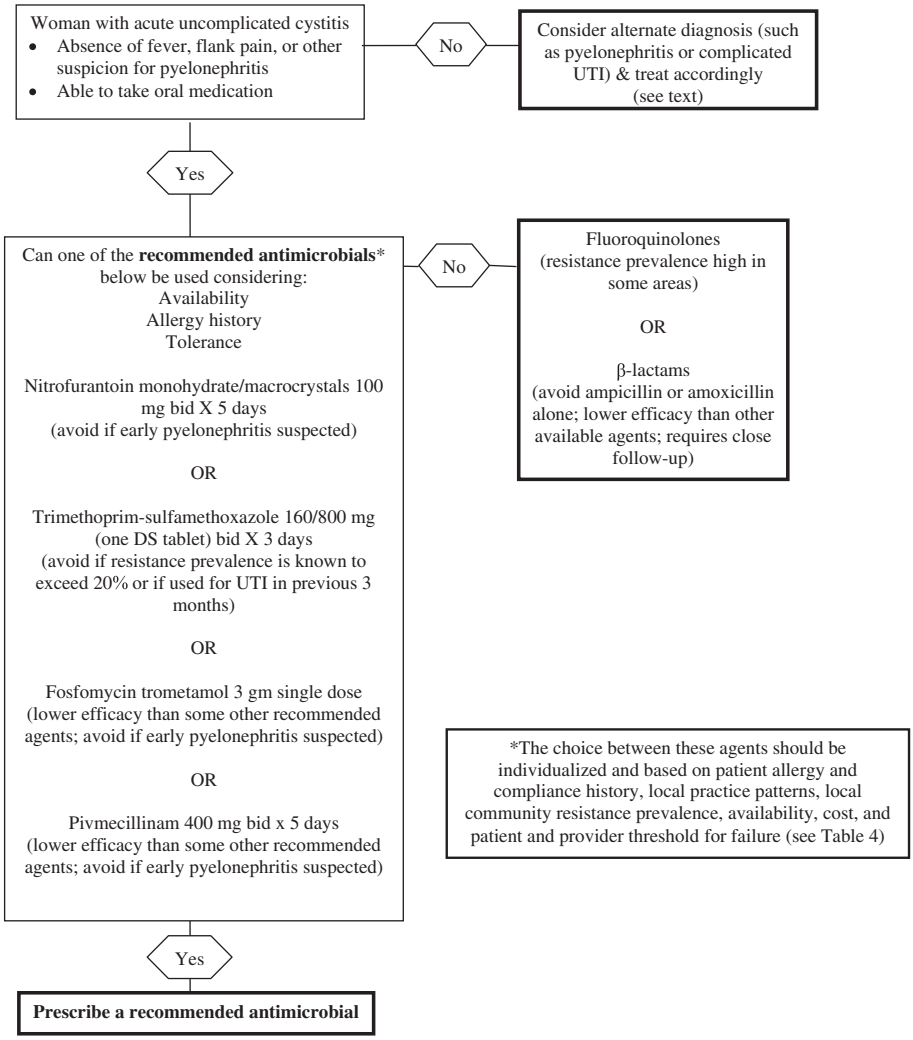


Figure 1. Approach to choosing an optimal antimicrobial agent for empirical treatment of acute uncomplicated cystitis. DS, double-strength; UTI, urinary tract infection.

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

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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].

iii. 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].

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. β-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 β-lactams, such as cephalexin, are less well studied but may also be appropriate in certain settings (B-III). The β-lactams generally have inferior efficacy and more adverse effects, compared with other UTI antimicrobials (B-I). For these reasons, β-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).

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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 β-lactam agents are less effective than other available agents for treatment of pyelonephritis (B-III). If an oral β-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 β-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).

INTRODUCTION

The focus of this guideline is management of women with acute uncomplicated cystitis and pyelonephritis who are not pregnant and have no known urological abnormalities or co-morbidities. An optimal approach to therapy includes consideration of antimicrobial resistance and collateral damage.

Consideration of Antimicrobial Resistance

The microbial spectrum of uncomplicated cystitis and pyelonephritis consists mainly of *Escherichia coli* (75%–95%), with occasional other species of Enterobacteriaceae, such as *Proteus mirabilis* and *Klebsiella pneumoniae,* and *Staphylococcus saprophyticus*. Other gram-negative and gram-positive species are rarely isolated in uncomplicated UTIs. Therefore, local antimicrobial susceptibility patterns of *E. coli* in particular should be considered in empirical antimicrobial selection for uncomplicated UTIs. Since the resistance patterns of *E. coli* strains causing uncomplicated UTI varies considerably between regions and countries, a specific treatment recommendation may not be universally suitable for all regions or countries.

Active surveillance studies of in vitro susceptibility of uropathogens in women with uncomplicated cystitis are helpful in making decisions about empirical therapy. Four large studies reporting in vitro susceptibility of *E. coli* causing uncomplicated UTI in North America and Europe were reviewed [8–11]. All of these demonstrate considerable geographic variability in susceptibility. For example, resistance rates for all antimicrobials were higher in US medical centers than in Canadian medical centers and were usually higher in Portugal and Spain than other European countries. In general, resistance rates >20% were reported in all regions for ampicillin, and in many countries and regions for trimethoprim with or without sulfamethoxazole. Fluoroquinolone resistance rates were still <10% in most parts of North America and Europe, but there was a clear trend for increasing resistance compared with previous years. Moreover, the resistance data for nalidixic acid in these studies suggest that >10% (in some countries, >20%) of the *E. coli* strains have acquired resistance genes for quinolones [10, 11]. First- and second-generation oral cephalosporins and amoxicillin-clavulanic acid also show regional variability, but the resistance rates were generally <10%. Despite wide variability in antimicrobial susceptibility among the different countries studied, nitrofurantoin, fosfomycin, and mecillinam (the latter 2 not tested in the Canadian study) had good in vitro activity in all the countries investigated. Thus, these 3 antimicrobials could be considered appropriate antimicrobials for empirical therapy in most regions [8–11]. Given a trend toward increasing resistance, compared with previous years, for most antimicrobials, continued monitoring of this data to evaluate rates over time is necessary for sustained optimization of empirical therapy [12].

Because local in vitro resistance rates are not always known, and change over time is anticipated, identification of individual predictors of resistance can also be useful to informing empirical antimicrobial choice. In 2 studies evaluating epidemiological predictors of resistance, the use of trimethoprim-sulfamethoxazole in the preceding 3–6 months was an independent risk factor for trimethoprim-sulfamethoxazole resistance in women with acute uncomplicated cystitis [13, 14]. In addition, 2 US-based studies demonstrated that travel outside the United States in the preceding 3–6 months was independently associated with trimethoprim-sulfamethoxazole resistance [15, 16]. Predictors of resistance to other cystitis antimicrobials are not as well studied but in general support the findings that exposure to the drug or to an area with endemic resistance are important factors to consider [17, 18]. Local resistance rates reported in hospital antibiograms are often skewed by cultures of samples obtained from inpatients or those with complicated infection and may not predict susceptibilities in women with uncomplicated community-acquired infection, in whom resistance rates tend to be lower [18, 19]. Prospective and unbiased resistance surveillance of uncomplicated uropathogens at the local practice and/or health care system levels is critical for informing empirical antimicrobial decisions. In the absence of such

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data, use of individual-level predictors of resistance can be helpful.

Because treatment of acute uncomplicated cystitis is usually empirical, it is likely that some women will be treated with a drug that does not have in vitro activity against the uropathogen. As the population resistance prevalence of a specific agent increases, the likelihood of failure outweighs the benefits of using the drug empirically. For most agents, clinical and bacterial outcomes are not well studied for varying levels of resistance; thus, recommended thresholds for using alternative agents are based on expert opinion or secondary analyses of studies that include patients with isolates resistant to the study drugs. The most evidence in this regard is available for trimethoprim-sulfamethoxazole, for which clinical, in vitro, and mathematical modeling studies consistently suggest a 20% resistance prevalence for the threshold at which the agent is no longer recommended for treatment of acute cystitis [20, 21]. There are insufficient data for other cystitis antimicrobials to recommend resistance levels at which the likelihood of failure outweighs the potential benefits, and the decision will vary by individual practitioner discretion. For pyelonephritis, timely use of an agent with in vitro activity is essential to treat the infection and minimize progression. Thus, thresholds at which a broad-spectrum agent would be selected empirically followed by directed therapy or for avoiding selected agents because of anticipated in vitro resistance are set at a relatively low resistance prevalence. The recommendation of a 10% fluoroquinolone resistance prevalence as the threshold for using an alternative agent in conjunction with or in place of a fluoroquinolone for pyelonephritis is primarily based on expert opinion, because there are limited data to provide evidence-based guidance.

Consideration of Collateral Damage

Collateral damage, a term describing ecological adverse effects of antimicrobial therapy, such as the selection of drug-resistant organisms and colonization or infection with multidrug-resistant organisms, has been associated with use of broad-spectrum cephalosporins and fluoroquinolones [22, 23]. Use of broad spectrum cephalosporins has been linked to subsequent infection with vancomycin-resistant enterococci, extended-spectrum β-lactamase–producing *Klebsiella pneumoniae*, β-lactam-resistant Acinetobacter species, and *Clostridium difficile* [22]. Use of fluoroquinolones has been linked to infection with methicillin-resistant *S. aureus* and with increasing fluoroquinolone resistance in gram-negative bacilli, such as *Pseudomonas aeruginosa* [22]. The preserved in vitro susceptibility of *E. coli* to nitrofurantoin, fosfomycin, and mecillinam over many years of use suggests these antimicrobials cause only minor collateral damage [8, 10], perhaps because of minimal effects on normal fecal flora [24–26]. In contrast, increased rates of antimicrobial resistance have been demonstrated for antimicrobials that affect the normal fecal flora more significantly, such as trimethoprim, trimethoprim-sulfamethoxazole, quinolones, and ampicillin [26, 27].

For uncomplicated cystitis, there are 2 reasons why collateral damage merits consideration. First, there is minimal risk of progression to tissue invasion or sepsis. Moreover, studies of placebo for treatment of uncomplicated cystitis demonstrate that clinical cure can be achieved in 25%–42% of women who are not treated or are treated with a drug without in vitro activity against the uropathogen [28, 29]. Thus, spontaneous resolution may attenuate differences in clinical outcomes when a drug with 80% efficacy is compared with one with 95% efficacy. Of note, placebo therapy is associated with prolongation of symptoms as well as a small risk of progression to pyelonephritis, as demonstrated by the 1 woman out of 38 women treated with placebo in the study by Christiaens et al [28]. Thus, these data do not justify withholding antimicrobial therapy for treatment of acute cystitis. Secondly, uncomplicated UTI is one of the most common indications for antimicrobial exposure in an otherwise healthy population; very small increments in collateral damage repeated many times may in aggregate magnify the impact of collateral damage when it occurs. Although reducing inappropriate use of fluoroquinolones for respiratory infections could have a greater impact on fluoroquinolone resistance, limiting use for UTIs may also mitigate increasing fluoroquinolone resistance [30].

Clinical Questions Addressed for the 2010 Update

The Expert Panel addressed the following clinical questions in the 2010 update:

I. What is the optimal treatment for acute uncomplicated cystitis in adult nonpregnant, premenopausal women?

II. What is the optimal treatment for acute uncomplicated pyelonephritis in adult nonpregnant, premenopausal women?

PRACTICE GUIDELINES

"Practice guidelines are systematically developed statements to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances" [31]. High quality guidelines are clear, reliable and reproducible, flexible, and based on a multidisciplinary review of evidence [31]. They should improve quality of care and serve as educational tools.

METHODOLOGY

Panel Composition

The IDSA Standards and Practice Guidelines Committee (SPGC) in collaboration with European Society for Microbiology and Infectious Diseases (ESCMID) convened experts in the

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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 ⩾1 properly randomized, controlled trial
II	Evidence from ⩾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 [32].

management of patients with cystitis and pyelonephritis. A specific effort was made to include representatives from diverse geographic areas and a wide breadth of specialties, including urology, obstetrics and gynecology, emergency medicine, family medicine, internal medicine, and infectious diseases, with a goal of improving the generalizability and acceptance of the recommendations and subsequent incorporation into clinical practice.

Process Overview

The evaluation of evidence for each antimicrobial class used in treatment of cystitis and pyelonephritis was performed by 2 members of the panel. Each member was assigned at least one antimicrobial class to review. 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) [32]. This scale had been modified from the one used in the 1999 guideline.

The level of evidence rating (I, II, or III) for recommendations in this guideline refers to evidence of the antimicrobial's efficacy in randomized clinical trials. The strength of the recommendation (A, B, or C) refers to the panel's level of comfort in recommending the antimicrobial for the treatment of uncomplicated UTI and is based on the drug's efficacy in clinical trials, rates of in vitro resistance among urinary pathogens, and the drug's propensity to cause collateral damage and adverse effects. For example, the panel felt that fosfomycin and pivmecillinam should be listed as agents recommended for treatment of uncomplicated cystitis, along with nitrofurantoin and trimethoprim-sulfamethoxazole, even though they appear to be less efficacious clinically, because they do not appear to cause collateral damage. On the other hand, the panel was less enthusiastic about strongly recommending fluoroquinolones for acute cystitis, even though they have high clinical efficacy, because of concerns about collateral damage and the subsequent threat to the usefulness of fluoroquinolones for the treatment of other more serious infections, including pyelonephritis.

It should be emphasized that, as is true with any treatment guideline, an assessment of the literature for a given agent's clinical efficacy is limited by the comparators studied. For example, amoxicillin-clavulanate has been shown to be statistically significantly inferior to ciprofloxacin in a randomized trial recently published. On the other hand, in the only published randomized study of cefpodoxime, its clinical efficacy appears to be comparable to that of trimethoprim-sulfamethoxazole. It is not clear how amoxicillin-clavulanate would compare with cefpodoxime or to trimethoprim-sulfamethoxazole.

Literature Review and Analysis

For the update, the Expert Panel completed a review and analysis of data published since 1998. Computerized literature searches of the Pubmed database were performed. The searches of the English-language literature from 1998 thru 2008, using the terms, cystitis or pyelonephritis with MESH terms of "acute uncomplicated UTI," "women," and specific antimicrobials and or classes of antimicrobials. To be included, the study had to be an open-label or randomized, clinical trial of treatment of women with symptoms of acute uncomplicated cystitis or pyelonephritis. At least 1 follow-up visit assessing microbiological or clinical response was required. Studies including >10% men or patients with complicated UTI were excluded. Non–English-language studies were excluded because they could not be reliably reviewed by panel members.

Outcomes of interest included early (first visit after treatment, typically occurring at 0–7 days after the last dose of the antimicrobial) clinical and microbiological cure, late (last visit after treatment, typically occurring 30–45 days after the last dose of the antimicrobial) clinical cure, and adverse effects.

Guidelines and Conflict of Interest

All members of the Expert Panel complied with the IDSA policy on conflicts of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the Expert Panel were

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provided IDSA's conflict of interest disclosure statement and were asked to identify ties to companies developing products that might be affected by promulgation of the guideline. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The panel made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict. Potential conflicts are listed in the Acknowledgements section.

Consensus Development Based on Evidence

The Panel met on 7 occasions via teleconference and once in person to complete the work of the guideline. The purpose of the teleconferences was to discuss the questions to be addressed, make writing assignments and discuss recommendations. Most of the work was done with e-mail correspondence. All members of the panel participated in the preparation and review of the draft guideline. Feedback from external peer reviews was obtained. All collaborating organizations were also asked to provide feedback and endorse the guidelines. The following organizations endorsed the guidelines: 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 guideline was reviewed and approved by the IDSA SPGC, the IDSA Board of Directors, and the ESCMID Board prior to dissemination.

Revision Dates

At annual intervals, the Panel Chair, the SPGC liaison advisor, and the Chair of the SPGC will determine the need for revisions to the guideline based on an examination of current literature. If necessary, the entire Panel will be reconvened to discuss potential changes. When appropriate, the panel will recommend revision of the guideline to the IDSA SPGC and Board and other collaborating organizations for review and approval.

RESULTS

Literature Search

The literature search identified 295 potential articles for review, of which 28 met criteria for inclusion in the analyses. The types of studies included randomized clinical trials and open label clinical trials. Expert reviews were also incorporated into the final grade recommendation. Two panel members were assigned each antimicrobial class included in the guideline and independently reviewed the relevant literature. These 2 reviewers compared their results and reached consensus on their findings for the antimicrobial class and then presented them to the panel. Discrepancies were discussed by the panel and final adjudication was based on review by the chairperson and majority vote.

Limitations in the Literature

There were a limited number of publications directly comparing the same drug given for different durations of therapy [29, 33]. Thus, there was insufficient new literature to support further analyses of single-dose or 3-day therapy versus longer therapy included in the previous guideline.

The criteria used to define clinical and microbiological cure and the duration of follow-up and timing of follow-up visits were not uniform across studies. Many studies did not perform or report intent to treat analyses; this may inflate the late clinical and microbiological success rates. Major differences in definitions of study outcomes are highlighted in the text.

GUIDELINE RECOMMENDATIONS FOR THE TREATMENT OF ACUTE UNCOMPLICATED CYSTITIS AND PYELONEPHRITIS

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].

iii. 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].

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

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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. β-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 β-lactams, such as cephalexin, are less well studied but may also be appropriate in certain settings (B-III). The β-lactams generally have inferior efficacy and more adverse effects, compared with other UTI antimicrobials (B-I). For these reasons, β-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).

Evidence Summary

The optimal agent for therapy of a patient with acute uncomplicated cystitis depends on a number of factors (Figure 2). Each agent has pros and cons related to its use and the choice of therapy is made on an individual basis.

Trimethoprim-sulfamethoxazole. The traditional first-line agent in the United States and recommended in the original IDSA guidelines was trimethoprim-sulfamethoxazole (trimethoprim was considered comparable) [1]. However, rising rates of trimethoprim-sulfamethoxazole resistance among uropathogens, especially outside of the United States, and consistent evidence that in vitro resistance correlates with bacterial and clinical failures, necessitates revising this recommendation. Indeed, the guidelines of the European Association of Urology do not recommend this agent as first choice treatment of uncomplicated cystitis [34].

Four randomized clinical trials compared trimethoprim-sulfamethoxazole with another agent, including ciprofloxacin, norfloxacin, nitrofurantoin, and cefpodoxime proxetil, and evaluated microbiological and clinical outcomes among women with acute cystitis (Table 2) [35–38]. The 2 studies including a fluoroquinolone had findings consistent with the 1999 guideline, reporting that trimethoprim-sulfamethoxazole was noninferior (95% confidence interval of difference at ±10%) to ciprofloxacin for early clinical and bacterial cure rates [35, 37]. Both studies used a longer than standard (7 days rather than 3 days) course of trimethoprim-sulfamethoxazole versus a 3-day course of ciprofloxacin. In the study by Iravani et al [37], 7 days of 160/800 mg twice-daily trimethoprim-sulfamethoxazole in 174 women had similar rates of early and late clinical cure as 3 days of 100 mg ciprofloxacin given twice daily to 168 women (95% early and 90% late for each drug). The late bacterial cure rate (4-6 weeks after therapy) was lower with trimethoprim-sulfamethoxazole than for ciprofloxacin (79% vs 91%, respectively), whereas the early bacterial cure rate was higher with trimethoprim-sulfamethoxazole (93% vs 88%, respectively). Arredondo-Garcia et al [35] reported that 7 days of trimethoprim-sulfamethoxazole (160/800 mg twice daily) in 81 women resulted in early clinical and bacterial cure rates of 86% and 85%, respectively, noninferior to the 89% and 92% cure rates, respectively, achieved in 97 women treated with 3 days of ciprofloxacin (250 mg twice daily). Of note, these similar outcomes were demonstrated despite 15% of women in the trimethoprim-sulfamethoxazole arm having a pretherapy isolate resistant to the treatment drug, compared with only 1% of women in the ciprofloxacin arm. Results stratified by susceptibility of the infecting organism to the treatment regimen were not reported. Each study included a third treatment arm; results of these comparisons are discussed below for the relevant antimicrobial class.

A small study compared a 3-day course of trimethoprim-sulfamethoxazole (160/800 mg twice daily) with a 3-day course of cefpodoxime-proxetil (100 mg twice daily) [38].

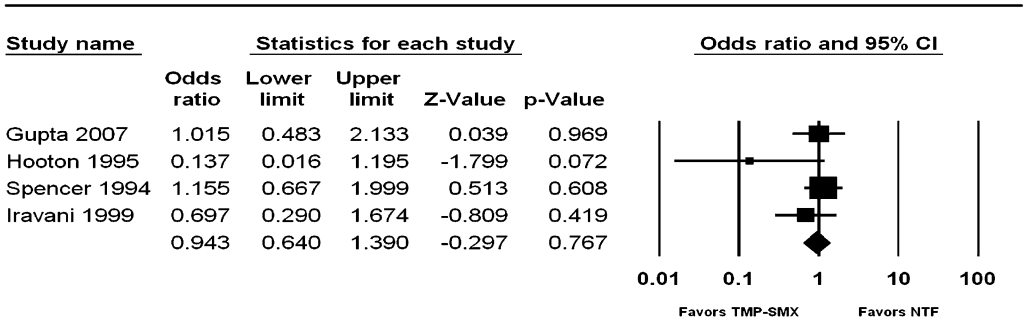


Figure 2. Meta-analysis of studies comparing trimethoprim-sulfamethoxazole (TMP-SMX) with nitrofurantoin (NTF) for acute uncomplicated cystitis. CI, confidence interval.

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Table 2. Results from Included Studies of Trimethoprim-Sulfamethoxazole for Treatment of Acute Uncomplicated Cystitis

Study (year) [reference]	Treatment regimen		
Iravani et al (1999) [37]	**TMP-SMX, 160/800 mg twice daily for 7 days**	**Nitrofurantoin monohydrate/ macrocrystals, 100 mg twice daily for 7 days**	**Ciprofloxacin, 100 mg twice daily for 3 days**
Early clinical cure	165/174 (95)	166/179 (93)	160/168 (95)
Early bacterial cure	161/174 (93)	153/177 (86)	148/168 (88)
Late clinical cure	137/153 (90)	135/151 (89)	132/147 (90)
Adverse events, %	38	34	28
Arredondo-Garcia et al (2004) [35]	**TMP-SMX, 160/800 mg twice daily x 7 days**	**Norfloxacin, 400 mgtwice daily for 7 days**	**Ciprofloxacin, 250 mg twice daily for 3 days**
Early clinical cure	70/81 (86)	90/107 (84)	86/97 (89)
Early bacterial cure	69/81 (85)	93/107 (87)	89/97 (92)
Late clinical cure	66/81 (82)	88/107 (82)	81/97 (84)
Adverse events, %	8.7	3.9	4.0
Kavatha et al (2003) [38]	**TMP-SMX, 160/800 mgtwice daily for 3 days**	**Cefpodoxime proxetil, 100 mg twice daily for 3 days**	
Early clinical cure	70/70 (100)	62/63 (98.4)	
Early bacterial cure	70/70 (100)	62/63 (98.4)	
Late clinical cure	51/60 (85)	42/50 (84)	
Adverse events, %	1.4	1.6	
Gupta et al (2007) [36]	**TMP-SMX, 160/800 mgtwice daily for 3 days**	**Nitrofurantoin monohydrate/ macrocrystals, 100 mg twice daily for 5 days**	
Early clinical cure	133/148 (90)	144/160 (90)	
Early bacterial cure	131/144 (91)	141/154 (92)	
Late clinical cure	117/148 (79)	134/160 (84)	
Adverse events, %	31	28%	

NOTE. Data are proportion of subjects (%), unless otherwise indicated. Efficacy rates refer to cure rates on the visit closest to a 5–9-day period following treatment. NA, not available; TMP-SMX, trimethoprim-sulfamethoxazole.

Women with an uropathogen resistant to either study drug (4 of 82 women in the trimethoprim-sulfamethoxazole arm and 0 of 81 women in the cefpodoxime arm) were excluded. Clinical cure was achieved in 100% of the 70 women in the trimethoprim-sulfamethoxazole arm, compared with 62 (98%) of 63 women in the cefpodoxime arm. The microbiological cure rates were the same as the clinical cure rates in each arm. Adverse effects were reported in 1 patient in the trimethoprim-sulfamethoxazole arm and 2 patients in the cefpodoxime arm.

The fourth study compared a 3-day course of trimethoprim-sulfamethoxazole (160/800 mg twice daily) with a 5-day course of nitrofurantoin monohydrate–macrocrystals (100 mg twice daily) and included women with uropathogens resistant to the study drugs [36]. The primary end point, overall clinical cure rate at 30 days, was 79% among the 148 women in the trimethoprim-sulfamethoxazole arm and 84% among the 160 women in the nitrofurantoin arm, with a nonsignificant difference of -5%. Rates were also equivalent (predefined as a $\pm$10% difference between agents) at 5-9 days after therapy, with clinical cure of 90% in each arm and bacterial cure of 91% in the trimethoprim-sulfamethoxazole arm and 92% in the nitrofurantoin arm. There was a significantly higher clinical cure rate among women in the trimethoprim-sulfamethoxazole arm who had a trimethoprim-sulfamethoxazole–susceptible uropathogen, compared with those who had a trimethoprim-sulfamethoxazole–resistant uropathogen (84% vs 41%, respectively;1 $P < .001$).

The fifth study used a prospective observational trial design to compare clinical and bacterial outcomes among women with acute cystitis with a trimethoprim-sulfamethoxazole–susceptible or –resistant uropathogen [21]. All women were treated with a 5-day course of trimethoprim-sulfamethoxazole (160/800 mg twice daily). The microbiological cure rates

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were significantly higher among women with a trimethoprim-sulfamethoxazole–susceptible uropathogen than for women with a –resistant uropathogen (86% vs 42%, respectively; $P < .001$). The clinical cure rate at 5-9 days after completion of therapy was also higher in the trimethoprim-sulfamethoxazole–susceptible group (88% of 333 women) than in the trimethoprim-sulfamethoxazole–resistant group (54% of 151 women; $P < .001$). The clinical and microbiological differences remained significant at the 28–42-day follow-up visit. Because this was not a randomized treatment trial, the data were not included in the efficacy analyses but are reported as they provide insight into expected outcomes in patients with resistant uropathogens.

Overall findings from these studies demonstrate that trimethoprim-sulfamethoxazole remains a highly effective treatment for acute uncomplicated cystitis in women when the rate of resistance is known or expected to be < 20%, supporting a strong recommendation for use in such settings. Early clinical and microbiological cure rates are in the 90% - 100% range (Table 2). Late outcomes are harder to compare across studies, but when calculated using intent to treat criteria, are 80% - 90%.

Resistance impacts both clinical and bacterial outcomes, so known or expected resistance should be considered in antimicrobial choice. In this regard, resistance to trimethoprim-sulfamethoxazole is high in many regions of the world. However, in settings with a 10% - 15% prevalence of resistance to trimethoprim-sulfamethoxazole, cure rates with trimethoprim-sulfamethoxazole were equivalent to those with comparator drugs (ie, ciprofloxacin and nitrofurantoin) to which almost all isolates were probably susceptible (data on susceptibility to comparators were not uniformly provided in the studies) [35–37]. Trimethoprim-sulfamethoxazole use is associated with increased resistance, but, even though it has a significant impact on intestinal flora, it is generally not thought to have a propensity for "collateral damage" as observed with broad-spectrum cephalosporins or fluoroquinolones.

Nitrofurantoin. There is additional evidence in support of nitrofurantoin monohydrate/macrocrystals, for which data were previously limited. There were 4 randomized trials of nitrofurantoin versus a comparator published since the previous guideline (Table 3) [28, 36, 37, 39]. These studies demonstrate that (1) nitrofurantoin monohydrate/

Table 3. Results from Included Studies of Nitrofurantoin for Treatment of Acute Uncomplicated Cystitis

Study	Regimen		
Iravani et al (1999) [37]	**Nitrofurantoin monohydrate/ macrocrystals, 100 mg twice daily for 7 days**	**TMP-SMX, 160/800 mg twice daily for 7 days**	**Ciprofloxacin, 100 mg twice daily for 3 days**
Early clinical cure	166/179 (93)	165/174 (95)	160/168 (95)
Early bacterial cure	153/177 (86)	161/174 (93)	148/168 (88)
Late clinical cure	135/151 (89)	137/153 (90)	132/147 (90)
Adverse events, %	34	38	28
Stein et al (1999) [39]	**Nitrofurantoin monohydrate/ macrocrystals, 100 mg twice daily for 7 days**	**Fosfomycin trometamol, single 3-gdose**	
Early clinical cure	232/245 (95)	240/263 (90)	
Early bacterial cure	189/219 (86)	192/246 (78)	
Late clinical cure	168/180 (93)	189/202 (94)	
Adverse events, %	5.6	5.3	
Christiaens et al (2002) [28]	**Nitrofurantoin macrocrystals, 100 mg 4 times daily for 3 days**	**Placebo, 4 times daily for 3 days**	
Early clinical cure	21/24 (88)	13/23 (54)	
Early bacterial cure	17/23 (74)	9/22 (41)	
Late clinical cure	NA	NA	
Adverse events, %	23	26	
Gupta et al (2007) [36]	**Nitrofurantoin monohydrate/ macrocrystals, 100 mg twice daily for 5 days**	**TMP-SMX, 160/800 mg twice daily for 3 days**	
Early clinical cure	144/160 (90)	133/148 (90)	
Early bacterial cure	141/154 (92)	131/144 (91)	
Late clinical cure	134/160 (84)	117/148 (79)	
Adverse events, %	28	31	

NOTE. Data are proportion of subjects (%), unless otherwise indicated. Efficacy rates refer to cure rates on the visit closest to a 5–9-day period following treatment. NA, not available; TMP-SMX, trimethoprim-sulfamethoxazole.

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macrocrystals (100 mg twice daily for 7 days) has similar clinical cure rates (based on the small differences in early clinical cure and confidence intervals that are small enough to suggest no difference in efficacy) to ciprofloxacin (100 mg twice daily for 3 days; 93% vs 95%), trimethoprim-sulfamethoxazole (160/800 mg twice daily for 7 days; 93% vs 95%), and 3-g single-dose fosfomycin trometamol (89% vs 90%); (2) nitrofurantoin monohydrate/macrocrystals (100 mg twice daily in a 5-day regimen) is equivalent in clinical and microbiological cure rates to trimethoprim-sulfamethoxazole (160/800 mg twice daily in a 3-day regimen); and (3) nitrofurantoin macrocrystals (100 mg 4 times daily for 3 days) is superior to placebo treatment of women with acute cystitis. Taken together, the studies demonstrate a clinical cure rate with nitrofurantoin of 88% - 93% and a bacterial cure rate of 81% - 92%. A meta-analysis of studies comparing early clinical cure rates with nitrofurantoin and trimethoprim-sulfamethoxazole is shown in Figure 2 and demonstrates equivalence between the 2 agents. Of note, resistance to nitrofurantoin remains low and it is well tolerated and efficacious in a 5-day regimen (Table 4).

Thus, current randomized clinical trial data provide strong support for consideration of nitrofurantoin as an effective agent for treatment of acute cystitis. Demonstration of efficacy, with minimal drug resistance or propensity for collateral damage, makes nitrofurantoin an attractive agent for cystitis. A 5-day regimen, rather than the traditional 7-day course, can be considered as an effective duration of treatment based on a recent randomized clinical trial [36].

Fosfomycin trometamol. There are also new data in support of fosfomycin trometamol, a phosphonic acid derivative available in the United States and some European countries for treatment of UTI. A 3-g single-dose of fosfomycin trometamol was compared with a 7–day course of nitrofurantoin monohydrate/macrocrystals 100 mg twice daily in one study and with a 5-day course of trimethoprim 100 mg twice daily in another [39, 40]. The latter study only evaluated the microbiologic outcome and reported that single-dose fosfomycin trometamol and 5 days of twice-daily trimethoprim each had an 83% bacterial cure rate (147 of 177 fosfomycin and 70 of 84 trimethoprim-treated women, respectively) at the early follow-up visit [34]. The study by Stein [39] demonstrated that the early clinical response (cure or improvement at 5-11 days after starting therapy) rates were not significantly different, at 91% (240 of 263 women) for 3-g single-dose fosfomycin trometamol treatment and 95% (232 of 245 women) for 100 mg of nitrofurantoin monohydrate/macrocrystals given twice daily. The late clinical response rates remained high for both drugs (93%–94%). However, the microbiologic cure rate was significantly higher with nitrofurantoin (86%), compared with fosfomycin (78%), at the first follow-up visit ($P = .02$). Microbiologic cure rates 4-6 weeks after therapy were 96% for fosfomycin and 91% for nitrofurantoin but

Table 4. Treatment Regimens and Expected Early Efficacy Rates for Acute Uncomplicated Cystitis

	Mean percentage (range)			
Drug (dosage)	Estimated clinical efficacy[ab]	Estimated microbiological efficacy[b]	Common side effects	References
Nitrofurantoin monohydrate/ macrocrystals (100 mg twice daily for 5–7 days)	93 (84–95)	88 (86–92)	Nausea,headache	[36, 37, 39]
Trimethoprim-sulfamethoxazole (160/800 mg twice daily for 3 days)	93 (90–100)	94 (91–100)	Rash, urticaria,nausea, vomiting, hematologic	[36, 37]
Fosfomycin trometamol (3 g single-dose sachet)	91	80 (78–83)	Diarrhea, nausea,headache	[39, 40]
Pivmecillinam (400 mg twice daily for 3–7 days)	73 (55–82)	79 (74–84)	Nausea, vomiting, diarrhea	[29, 43]
Fluoroquinolones (dose varies by agent; 3–day regimen)[c]	90 (85–98)	91 (81–98)	Nausea/vomiting, diarrhea, headache, drowsiness, insomnia	[35, 43, 44, 46–52]
β-lactams (dose varies by agent; 3–5 day regimen)[d]	89 (79–98)	82 (74–98)	Diarrhea, nausea, vomiting, rash, urticaria	[38, 52, 54]

[a] Efficacy rates refer to cure rates on the visit closest to a 5–9-day period following treatment, and are averages or ranges calculated from clinical trials discussed in the text.

[b] Estimated clinical efficacy and microbiological efficacy rates should not necessarily be compared across agents, because study design, efficacy definition, therapy duration, and other factors are heterogeneous. Studies represent clinical trials published since publication of the 1999 Infectious Disease Society of America guidelines so as to represent efficacy rates that account for contemporary prevalence of antibiotic-resistant uropathogens. Note that efficacy rates may vary geographically depending on local patterns of antimicrobial resistance among uropathogens. See text for details.

[c] Data on fluoroquinolones are compiled from regimens of ofloxacin, norfloxacin, and ciprofloxacin from the referenced clinical trials and not other fluoroquinolones that are no longer commercially available. See text for details.

[d] Data on βlactams data cited are derived from clinical trials examining second and third generation cephalosporins and amoxicillin-clavulanate. See text for details.

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included only ~50% of the original study population. Intent–to-treat analyses were not reported [39]. Overall, the bacterial efficacy of fosfomycin is lower than that of other first-line agents, but clinical efficacy (based on a single study) was comparable (Table 4). Additional information considered by the committee was the reference in the 1999 IDSA UTI guideline to unpublished data demonstrating lower bacterial eradication rates with fosfomycin than with 10 days of trimethoprim-sulfamethoxazole and with 7 days of ciprofloxacin. These studies are still not available in the published literature except as previously referenced in a Medical Letter report [7].

Several in vitro studies examined the activity of fosfomycin against multidrug-resistant pathogens. These demonstrate that fosfomycin is active against vancomycin-resistant enterococci (VRE), methicillin-resistant *S. aureus* (MRSA), and extended-spectrum β-lactamase (ESBL)–producing gram-negative rods [41]. As resistance among uropathogens causing community-acquired uncomplicated cystitis increases, fosfomycin may become more useful, particularly if no other oral agents with in vitro activity are available [42]. Clinical outcomes are not yet reported from randomized, controlled studies; thus, specific recommendations for the role of fosfomycin in the treatment of multidrug-resistant uropathogens cannot be included in the current guideline. However, observational studies are supportive of clinical efficacy [41, 42].

The convenience of a single-dose regimen, in vitro activity against resistant gram-negative rods, and minimal propensity for collateral damage make fosfomycin a useful choice in some areas. It is recommended as a first-line agent in the guidelines of the European Association of Urology, although it is not uniformly available [34]. Susceptibility data are also not uniformly available, because testing is not routinely performed in many clinical laboratories. Furthermore, the effect of fosfomycin on the intestinal flora after intake of a single 3-g dose (the standard dosage for uncomplicated UTI) has not been well studied, but the effect is probably minor [25]. This assumption is supported by the high rate of *E. coli* susceptibility in regions with frequent use of fosfomycin for uncomplicated cystitis in women [10].

Pivmecillinam. Pivmecillinam, the orally bioavailable form of mecillinam, is distinguished from other β-lactams because of its specificity for the urinary tract, minimal resistance or propensity for collateral damage, and reasonable treatment efficacy. It is an extended gram-negative spectrum penicillin used only for treatment of UTI. Two studies met our inclusion criteria [43]. One study compared different doses of pivmecillinam with placebo. Pivmecillinam at 200 mg 3 times daily for 7 days, 200 mg twice daily for 7 days, and 400 mg twice daily for 3 days resulted in early clinical cure rates of 62% (132 of 217 women), 64% (136 of 220 women), and 55% (119 of 220 women), respectively, and bacteriologic cure rates of 93%, 94%, and 84%, respectively. Placebo therapy resulted in a clinical cure rate of 25% (54 of 227 women) and a bacteriologic cure rate of 34%, both inferior to active drug. In another randomized trial comparing 3 days of pivmecillinam (400 mg bid) with 3 days of norfloxacin (400 mg bid), pivmecillinam treatment resulted in lower bacterial cure rates (222 (75%) of 298 vs 276 (91%) of 302, respectively; $P < .001$) and lower clinical cure rates (360 (82%) of 437 vs 381 (88%) of 433, respectively; $P = .02$) [43]. In vitro resistance to pivmecillinam was not associated with a high rate of failure; 30 (88%) of 34 pivmecillinam-treated patients who had a pivmecillinam-resistant uropathogen achieved bacterial cure.

Although not available in the United States or Canada, pivmecillinam is one of the agents of choice in many Nordic countries due to low resistance rates and low propagation of resistance [24]. Different doses and durations have been associated with varying efficacy rates, and a 5-day or 7-day regimen is probably superior to a 3-day regimen. Similarly, a 400-mg dose fared better than a 200-mg dose for both bacterial and clinical efficacy. The efficacy rates are notably lower than other recommended agents (Table 4). Of note, the rate of resistance among *E. coli* to pivmecillinam remains low despite its frequent use in some European countries [24].

Fluoroquinolones. There were 12 randomized trials of fluoroquinolones for treatment of acute cystitis. The majority of these compared one fluoroquinolone with another, often in varying doses or durations. Sparfloxacin and gatifloxacin are no longer widely available because of their adverse effects, and thus, results related to these 2 agents are not included in the analyses [44–47]. Two large studies compared 500 mg of extended-release once-daily ciprofloxacin to the 250-mg twice-daily formulation of ciprofloxacin and demonstrated equivalent cure rates [48, 49]. Another study compared ciprofloxacin (250 mg twice daily) in a 3-day versus a 7-day regimen and demonstrated equivalent cure rates but significantly higher adverse event rates with the longer regimen [50]. A small study compared norfloxacin 400 mg twice daily with norfloxacin 800 mg once daily and demonstrated similar bacterial and clinical outcomes, albeit with limited power to detect true differences [33]. One study compared single-dose ciprofloxacin with 3 days of norfloxacin and found the agents to be equivalent, with microbiological and clinical cure rates in the 91% - 94% range [51].

Three studies compared a fluoroquinolone with a drug from another class. Two demonstrated better clinical and microbiological cure rates with the fluoroquinolone regimen (norfloxacin vs pivmecillinam and ciprofloxacin vs amoxicillin-clavulanate) [43, 52]. The third demonstrated early clinical and bacterial cure rates to be similar with 3 days of low-dose ciprofloxacin or a standard dose but longer duration (7 days each) of trimethoprim-sulfamethoxazole and nitrofurantoin [37]. The details for each of these studies are discussed under the respective comparator agent. Overall clinical and bacterial

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efficacy rates in the studies are consistently high, although they were occasionally <90% (Table 4).

Thus, fluoroquinolones remain very effective for the treatment of acute cystitis, although increased fluoroquinolone resistance among community uropathogens is mitigating the usefulness of this antimicrobial class. Once-daily dosing of ciprofloxacin is now available and of equal efficacy as the twice-daily formulation, albeit more expensive, since the latter is now generic. Single-dose fluoroquinolone therapy remains an option but with possibly lower efficacy rates than with longer regimens [1]. Fluoroquinolones with longer half-lives, such as pefloxacin and fleroxacin, may be useful for single-dose therapy, but no studies met our eligibility criteria and neither agent is available in all locales, including North America and many parts of Europe. The main concern regarding fluoroquinolone use for acute cystitis is the promotion of fluoroquinolone resistance, not only among uropathogens but also other organisms, causing more serious and difficult–to-treat infections at other sites. There is also concern about the association between fluoroquinolone use and increased rates of MRSA [22]. Many experts now call for restricting use of fluoroquinolones to those episodes of uncomplicated cystitis when other UTI antimicrobials are not suitable [53]. The panel agrees and recommends that fluoroquinolones be reserved as an alternative only when other UTI agents cannot be used (Figure 1).

β-*Lactams.* Five randomized trials evaluating β-lactam antibiotics were identified and included in the analyses. Only 1 study included a 3-day regimen of trimethoprim-sulfamethoxazole as the standard comparator [38]. This study demonstrated that 100 mg of cefpodoxime proxetil twice daily for 3 days was equivalent to trimethoprim-sulfamethoxazole (160/800 mg twice daily for 3 days), with 100% of 70 women treated with trimethoprim-sulfamethoxazole and 98% of 63 women treated with cefpodoxime experiencing clinical and microbiological cured at day 4–7 after completion of therapy. Clinical cure at 28 days was somewhat lower but not different between the treatment arms (Table 2). However, the statistical power of the study to find differences between the drugs was limited by its small sample size. Side effects were not different between the 2 groups. In another study, amoxicillin-clavulanate (500/125 mg twice daily) was compared with ciprofloxacin (250 mg twice daily), both for 3 days, with 4 months of follow-up [52]. Clinical cure at the last follow-up visit was observed in 58% of 160 women treated with amoxicillin-clavulanate, compared with 77% of 162 women treated with ciprofloxacin ($P < .001$). The differences were significant even among the subgroups of women infected with strains susceptible to the treatment drug (60% vs 77%, respectively; $P = .004$). Microbiological cure at 2 weeks was observed in 76% of 156 women treated with amoxicillin-clavulanate, compared with 95% of 161 women treated with ciprofloxacin ($P < .001$) [52]. Vaginal colonization with uropathogens before and after therapy was also measured, and the higher clinical failure rate observed with amoxicillin-clavulanate was associated with a lower rate of eradication of vaginal uropathogens in the amoxicillin-clavulanate group. These findings are consistent with the postulated mechanism for β-lactam inferiority in the treatment of UTI being, in part, related to persistence of the vaginal reservoir for infection. Another study compared 2 β-lactam antibiotics, cefdinir (100 mg twice daily) versus ceflacor (250 mg 3 times daily), each for 5 days, and demonstrated equivalent clinical (91% vs 93%, respectively) and microbiological (85% vs 80%, respectively) cure rates [54].

Thus, the overall evidence of the efficacy of β-lactams for treatment of acute cystitis has not changed since the previous guideline [1]. Most studies demonstrate that β-lactams are generally inferior in cure rates to the fluoroquinolones [42, 52]. The study by Kavatha et al [38] demonstrating that an advanced generation oral cephalosporin (cefpodoxime proxetil) resulted in cure rates equivalent to those of trimethoprim-sulfamethoxazole is intriguing and needs to be confirmed in a larger clinical trial [38]. However, even if these observations are confirmed, concern about emergence of gram-negative ESBL resistance to these agents limits enthusiasm for any widespread use. Broad-spectrum cephalosporins, in particular, have been associated with collateral damage, the most concerning of which is ESBL resistance among gram-negative bacteria [22]. Narrower-spectrum cephalosporins are often used for treatment of UTI and may result in less collateral damage, compared with broad-spectrum cephalosporins; however, there is a lack of adequately powered studies to make specific recommendations for these agents. Thus, the panel feels that currently available data supports avoidance of β-lactams other than pivmecillinam for empirical therapy of uncomplicated cystitis unless none of the recommended agents are appropriate.

The choice of agent should be individualized on the basis of patient allergy and compliance history, local practice patterns, local community resistance prevalence, availability, cost, and patient and provider threshold for failure. In the event of diagnostic uncertainty regarding cystitis versus early pyelonephritis, use of agents such as nitrofurantoin, fosfomycin, and pivmecillinam should be avoided, because they do not achieve adequate renal tissue levels. Such uncertainly may exist in the setting of cystitis symptoms accompanied by subjective fever that is not verified at the time of examination, a prolonged duration of cystitis symptoms (typically greater than 5–7 days), or vague flank pain or tenderness which is not otherwise explained.

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

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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 gof 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 β-lactam agents are less effective than other available agents for treatment of pyelonephritis (B-III). If an oral β-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 β-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).

Evidence Summary

Optimal therapy for acute uncomplicated pyelonephritis depends on the severity of illness at presentation and local resistance patterns as well as specific host factors (such as allergies). In addition, urine culture and susceptibility testing should be performed, and initial empirical therapy should be tailored appropriately on the basis of the infecting uropathogen. Strategies for optimizing empirical therapy when local resistance patterns are not known include using an initial intravenous dose of a long-acting parenteral antimicrobial and starting with a broader-spectrum agent and narrowing therapy when laboratory results are available.

There were 6 treatment studies of acute uncomplicated pyelonephritis identified, but only 1 study met our inclusion criteria. This study compared a 7-day regimen of oral ciprofloxacin (500 mg twice daily) with a 14-day regimen of trimethoprim-sulfamethoxazole (160/800 mg twice daily) for treatment of women presenting to emergency departments or outpatient clinics with mild to moderate pyelonephritis [55]. An initial intravenous 400-mg dose of ciprofloxacin in the ciprofloxacin group or a 1-g dose of ceftriaxone in the trimethoprim-sulfamethoxazole group was allowed in the protocol at the discretion of the clinician. Women with an uropathogen resistant to the study drug to which they were randomized continued to receive the drug unless they experienced clinical failure (14 women in the trimethoprim-sulfamethoxazole group and 1 woman in the ciprofloxacin group). Ciprofloxacin had significantly higher microbiological (99% vs 89%, respectively) and clinical (96% vs 83%, respectively) cure rates at the early post-therapy visit. Cure rates were similar regardless of whether an initial intravenous dose of ciprofloxacin was given. Among trimethoprim-sulfamethoxazole–treated women, those with a trimethoprim-sulfamethoxazole–resistant uropathogen had significantly lower microbiological eradication and clinical cure rates, compared with those with a susceptible uropathogen. An initial intravenous dose of ceftriaxone significantly improved the microbiological eradication rate and moderately improved the clinical cure rate in women with a trimethoprim-sulfamethoxazole–resistant uropathogen.

Two additional studies also demonstrated that a 5–7-day regimen of a once-daily fluoroquinolone (ciprofloxacin, 1000 mg extended release, and levofloxacin, 750 mg, respectively) were effective for acute pyelonephritis [56, 57]. These studies did not meet our inclusion criteria because they included

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a mixed population of men and women with acute pyelonephritis and/or complicated UTIs, but they do lend additional support for a 5–7-day fluoroquinolone regimen versus the traditional 14-day regimen for mild to moderate pyelonephritis. A study of once-daily gatifloxacin (200 mg or 400 mg) was similar in design and outcomes but is not discussed further because the oral formulation is no longer available in most parts of the world [58]. Another pyelonephritis study demonstrated that 10 days of an oral fluoroquinolone (norfloxacin, 400 mg twice daily) resulted in lower bacterial relapse rates than did 10 days of ceftibuten (200 mg twice daily), with each group receiving intravenous cefuroxime for 2–4 days prior to randomization to the study drugs [59]. This study also included a mixed population of men and women and thus did not meet our inclusion criteria. Another study demonstrated that initial therapy with intravenous ceftriaxone (1 g for 3 days) was comparable to 1 dose of intravenous ceftriaxone (1 g) followed by oral cefixime (400 mg once daily for 2 days). Both groups received a 10-day course of an oral antibiotic on the basis of susceptibility test results after the initial regimen was completed [60].

The findings from the 1 study that met our specific inclusion and exclusion criteria as well as the additional studies described support the superior efficacy of fluoroquinolone regimens for treatment of acute pyelonephritis [55]. These studies also demonstrate efficacy of a 5–7-day regimen and once-daily dosing for mild to moderate pyelonephritis. In regions with low levels of fluoroquinolone resistance among outpatient uncomplicated pyelonephritis isolates, as demonstrated in 2 recent US studies, the fluoroquinolones are the preferred antimicrobial class for oral therapy [18, 61]. For some areas of the world, including certain areas of the United States, the prevalence of fluoroquinolone resistance is >10%. In such areas, it is recommended that a dose of a long-acting parenteral antimicrobial, such as a 1-g dose of ceftriaxone or a consolidated 24-h dose of an aminoglycoside (eg, one 5–7-mg/kg dose of gentamicin), be given once at the initiation of therapy. Some experts prefer to continue the parenteral agent until susceptibility data are available; this strategy is not well studied, but it can be considered depending on feasibility and clinical judgment. The parenteral agent may be administered via the intramuscular route if the intravenous route is not available, but there are limited data supporting this approach.

High rates of resistance to trimethoprim-sulfamethoxazole with corresponding failure rates for resistant isolates make this agent an inferior choice for empirical therapy, but it is highly efficacious in pyelonephritis if the causative organism is susceptible. The current efficacy rates observed for trimethoprim-sulfamethoxazole in the treatment of pyelonephritis are based on a 14-day regimen, which is the FDA-approved duration of treatment [55]. However, there are no data to suggest a shorter course of trimethoprim-sulfamethoxazole would not be effective when the uropathogen is susceptible, and additional studies of short-course regimens are warranted. If trimethoprim-sulfamethoxazole is used empirically, an initial intravenous dose of ceftriaxone is recommended as this combination resulted in improved clinical and bacterial cure rates in the study by Talan et al [55]. Although not formally studied, a consolidated 24-h dose of an aminoglycoside could also be considered in place of ceftriaxone.

Oral β-lactam agents should be used with caution for treatment of pyelonephritis, on the basis of studies outlined in the previous guideline demonstrating inferior efficacy and higher relapse rates compared with trimethoprim-sulfamethoxazole [1]. Those studies primarily evaluated aminopenicillins. Current data on oral cephalosporins are limited but are suggestive of inferior efficacy compared with the fluoroquinolones [59]. If an oral β-lactam is used, an initial intravenous dose of ceftriaxone or a consolidated 24-h dose of an aminoglycoside is recommended. Continued use of the oral β-lactam is reasonable only if the uropathogen is susceptible. Initial coadministration of a parenteral agent is supported in part by the findings of Sanchez et al [60], who reported similar outcomes with ‘ one dose of ceftriaxone versus a 3-day course of ceftriaxone followed by oral β-lactam therapy in women with uncomplicated pyelonephritis. As outlined in the previous guideline, a total course of 10–14 days of therapy is likely sufficient when using an oral β-lactam for treatment of uncomplicated pyelonephritis.

Uncomplicated cystitis or pyelonephritis due to MRSA is uncommon, and at this time, there are insufficient data to recommend use of an MRSA-active agent for empirical therapy of uncomplicated UTI. Recommendations for treatment of acute uncomplicated pyelonephritis that is accompanied by nausea or vomiting, which precludes oral intake or otherwise requires hospitalization, are the same as previously outlined in the 1999 IDSA guideline, because no new data are available to warrant revisions [1]. Given rising rates of ampicillin resistance among gram-negative organisms, the use of ampicillin should be limited to patients in whom *Enterococcus* infection is suspected as the pathogen (based on previous history) and should be accompanied by an aminoglycoside. Broad-spectrum antimicrobial coverage should be tailored, as appropriate, on the basis of urine culture and susceptibility results.

FUTURE DIRECTIONS AND RESEARCH GAPS IN MANAGEMENT OF ACUTE UNCOMPLICATED CYSTITIS AND PYELONEPHRITIS

As listed below, the panel identified several areas warranting further investigation.

- Better understanding of collateral damage in the treatment of uncomplicated cystitis.
- Better understanding of the public health impact of antimicrobial use and resistance in women with sporadic uncomplicated UTI.

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- Role of MRSA in uncomplicated cystitis and pyelonephritis.
- Efficacy of narrow-spectrum cephalosporins in treatment of uncomplicated cystitis.
- Role of oral broad-spectrum cephalosporins for outpatient treatment of pyelonephritis in regions with high prevalence of resistance to fluoroquinolones.
- Efficacy of short course (7–10 day) regimens with trimethoprim-sulfamethoxazole for pyelonephritis caused by a trimethoprim-sulfamethoxazole susceptible pathogen.
- Optimal therapy of acute cystitis in women who are postmenopausal or have well-controlled diabetes without urological sequelae.
- Better understanding of optimal treatment regimens for ESBL- producing uropathogens causing uncomplicated UTI.
- Additional studies of clinical efficacy rates achieved in the setting of an acute cystitis uropathogen that is resistant to the antimicrobial agent used for treatment.
- Prospective and unbiased resistance surveillance of uropathogens at the local practice and/or health care system level in order to best inform antimicrobial decisions.

PERFORMANCE MEASURES

Performance measures are indicators to help guideline users gauge potential effects and benefits of implementation of the guidelines. Such tools can be indicators of the actual process, short-term and long-term outcomes, or both. Deviations from the recommendations are expected in a proportion of cases, and compliance in 80%–95% of cases is generally appropriate, depending on the measure. The following measures were identified as appropriate indicators for management of acute uncomplicated UTI in women.

- Use of a recommended antimicrobial for treatment of uncomplicated cystitis in cases in which it is not prohibited because of allergy history or availability
- Use of fluoroquinolones for treatment of acute uncomplicated cystitis only when a recommended antimicrobial cannot be used
- Use of a recommended antimicrobial for treatment of uncomplicated pyelonephritis in cases in which it is not prohibited because of allergy history or availability
- Initiation of empirical therapy for acute uncomplicated pyelonephritis with performance of a pretherapy urine culture and modification of empirical therapy as indicated by culture results

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