# Managing Acute Uncomplicated Cystitis in Women in the Era of Antibiotic Resistance

THIS NEWSLETTER IS BASED ON A SERIES OF TELECONFERENCES CONDUCTED OCTOBER-DECEMBER 2003

PRESENTED BY

The Office on Women's Health of the U.S. Department of Health and Human Services

IN COOPERATION WITH:

American Medical Association
Physicians dedicated to the health of America

American Academy of Nurse Practitioners

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## TARGET AUDIENCE

Primary care physicians (family physicians, general practitioners, internal medicine physicians), obstetrician/gynecologists, nurse practitioners, physician assistants, nurse midwives, and other healthcare professionals who care for patients with acute uncomplicated cystitis.

## STATEMENT OF NEED

Acute uncomplicated cystitis (AUC) is a common urinary tract infection that affects women of all ages. Until recently, management of AUC has been fairly straightforward; however, the continuing growth of resistance to antibiotics among common pathogens necessitates ongoing reassessment of standard empiric therapy. Healthcare professionals who provide treatment to women with AUC need to be aware of the clinical implications of antibiotic resistance and its impact not only on treating AUC in individual patients but also on the use of antibiotics in treating other, more serious diseases.

## LEARNING OBJECTIVES

Upon completion of this program, the participant should be able to:

- Discuss the etiology and epidemiology of acute uncomplicated cystitis (AUC)
- List the risk factors for development and recurrence of AUC in women
- Review current pharmacologic and nonpharmacologic prevention strategies
- Describe the impact of the growth of antibiotic resistance on the management of AUC
- Identify the benefits and disadvantages of traditional and newer antimicrobial agents

## ACCREDITATION STATEMENT

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Minnesota and IMED Communications. The University of Minnesota is accredited by the ACCME to provide continuing medical education for physicians.

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### Nurse Practitioners

Approved by the Continuing Education Approval Program of the National Association of Nurse Practitioners in Women's Health for 1 contact hour, including 1 hour of pharmacology. Offering number 03-51.

### Physician Assistants

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### Nurse-Midwives

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- Topical estrogen therapies for the prevention of urinary tract infection
- All urinary tract infection therapies mentioned for prophylaxis
- Trimethoprim/sulfamethoxazole used for 3 days to treat uncomplicated urinary tract infection

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# Managing Acute Uncomplicated Cystitis in Women in the Era of Antibiotic Resistance

**This newsletter is based on a series of teleconferences held in late 2003**

## INTRODUCTION

Acute uncomplicated cystitis (AUC) affects many women and occurs throughout their lives. Women with AUC often have recurrent urinary tract infections (RUTIs). When UTIs recur frequently, they can have a significant negative impact on a woman's quality of life and productivity. This timely subject was addressed recently in a series of teleconferences led by an expert faculty; this newsletter summarizes the information presented in the teleconferences.

Bacterial resistance to antibiotics decreases the effectiveness of treatment and increases costs of treatment. Office-based prescribing of some antibiotics has decreased in the past few years, but prescribing of broad-spectrum agents, such as fluoroquinolones, has increased.[1] With this increased use comes the possibility of increasing resistance, leading to treatment failure.

Empiric treatment of AUC (lower UTI) is convenient and cost-effective. Clinicians can frequently diagnose AUC after the patient describes her symptoms over the telephone. Patients who have experienced UTIs can reliably identify new episodes. Clinicians will often prescribe treatment based on guidelines following telephone diagnosis. However, growing resistance to antibiotics among the most common uropathogens may limit the efficacy of empiric treatment.

An issue now being considered is whether current recommendations for empiric treatment of AUC should be modified to limit prescribing of broad-spectrum agents to preserve them for treating more serious infections. To accomplish this, clinicians would need to use agents whose efficacy in treating AUC is known and against which there is little bacterial resistance. Sometimes, efficacy and resistance must be balanced when regimens are compared.

This newsletter focuses on the treatment of acute uncomplicated cystitis and, with the exception of the subsection on *Treating UTI During Pregnancy*, is not intended to address the treatment of complicated UTI or of pregnant patients.

## UTI BASICS

### Definitions

#### *Uncomplicated UTI (AUC, lower UTI)*

A UTI is considered uncomplicated if it occurs in healthy women with no functional or structural abnormalities of the genitourinary tract.[2,3]

#### *Complicated UTI*

Patients with indwelling catheters, immunosuppressed patients, and patients with certain underlying diseases are considered to have complicated UTI, and people more than 65 years of age are also usually considered to have complicated UTI.[2,3] Patients who have had recent genitourinary tract instrumentation (such as cystoscopy), recipients of kidney transplants, and pregnant women are also usually considered to have complicated UTI. Because physicians often treat women throughout their adult lives, UTI during pregnancy (despite its being considered complicated) is specifically discussed later in this newsletter in the subsection *Treating UTI During Pregnancy*.

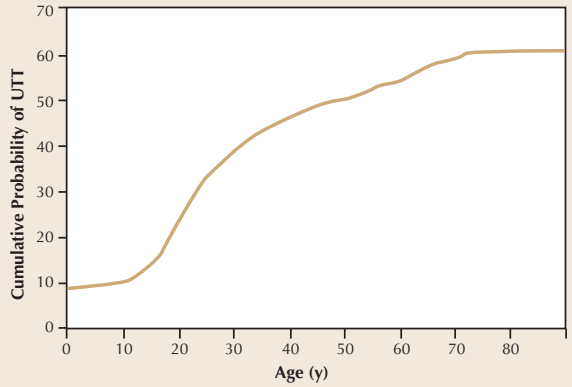
### Epidemiology

UTI is the most commonly occurring infection. Although it occurs more frequently in males in early infancy, UTI is much more common in females throughout the rest of life.[4] Forty percent to 50% of women will have at least 1 UTI in their lives.[5]

AUC occurs in 1% to 3% of young girls,[6] and the prevalence then increases every decade until menopause (Figure 1, page 2).[5] By 32 years of age, 1 of every 2 women will have had at least 1 UTI. The prevalence of significant bacteriuria is 8% to 10% in elderly women.[4,7] However, the majority of AUC occurs in young, sexually active women.

**FIGURE 1**

**Cumulative Probability of UTI Among US Women**




UTI=urinary tract infection.
Adapted from *Ann Epidemiol.*, Vol 10, Foxman B, Barlow R, D'Arcy H, Gillespie B, Sobel JD, Urinary Tract Infections: Self-Reported Incidence and Associated Costs, pages 509-515, Copyright 2000, with permission from Elsevier.

### Microbiology

By far the most common pathogen causing uncomplicated UTI is *Escherichia coli*, followed by *Staphylococcus saprophyticus* (Figure 2).[8,9] An antibiotic effective against these bacteria is necessary for treating uncomplicated UTI. Other pathogens *(Klebsiella, Proteus, Enterobacter* species, and group B streptococci) are uncommon causes of uncomplicated UTI.[8,9]

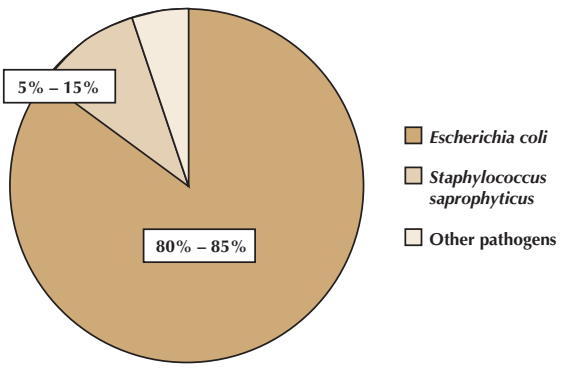
### Costs

Recent estimates of direct medical expenses related to AUC, including physician fees and medication, are approximated at $474 million per year. Direct nonmedical expenses, estimated to be about $185 million per year, include travel and childcare costs as well as income lost because of time taken off from work for medical visits. In addition, there are indirect costs of AUC, which include work time and income lost because of restricted activity and the costs of reduced unpaid productivity, such as not being able to perform household chores. These are estimated at $936 million, for a total annual cost of approximately $1.6 billion.[10]

The impact on decreased quality of life, of course, cannot be quantified. Optimal therapy would be therapy that is effective and can be instituted quickly based on symptoms to limit adverse effects and costs.

**FIGURE 2**

**Microbiology of Uncomplicated UTI[8,9]**




## RISK FACTORS

### Physical

There is a genetic propensity to recurrent AUC in women. Women with close female relatives who have had UTIs are at least 50% more likely to have UTIs themselves than are women without such a family history.[11] Women who experience RUTIs are also more likely to be nonsecretors of ABH blood group antigens than those who do not experience RUTIs.[12,13]

The loss of estrogen at menopause may alter the vaginal milieu, leading to reduced lactobacilli and increased pH with increased vaginal colonization by Enterobacteriaceae.[13]

### Behavioral

The incidence of UTI is highly associated with vaginal intercourse[13] and increases with more frequent intercourse. In addition, having new sexual partners is associated with an increased short-term risk for infection.[14]

The type of birth control a woman uses can also affect her risk of UTI. Among contraceptive methods, the use of spermicide—with diaphragms, with condoms, or alone—is the factor most closely linked to risk of UTI.[13,15] The use of birth control pills or condoms without spermicide is not associated with an increased risk of infection. A properly placed diaphragm may cause pressure on the bladder that leads to incomplete voiding and is associated with a small increased risk for infection.[16] The small risks posed by diaphragms alone, however, are magnified by the fact that they are almost always used with spermicide.

Recent use of antibiotics, whether or not for the treatment of UTI, has been shown to increase the risk of UTI as well. Smith et al suggest that recent antibiotic use may alter the urogenital flora and facilitate colonization with uropathogens.[17]

Certain behaviors previously thought to increase the risk of UTI have been found not to be risk factors. These behaviors include pre- and postcoital voiding patterns, frequency of urination, wiping patterns, douching, tampon use, choice of clothing[13,18,19] and bathing vs showering.

## DIAGNOSIS

### History and Physical

A patient's report of symptoms is the most reliable indicator of whether she has AUC.

The presence of dysuria, urinary frequency, hematuria, and low back pain are highly suggestive of AUC, whereas vaginal discharge or irritation favors an alternate diagnosis.[20]

Because AUC is reliably diagnosed based on history and symptoms, and because AUC is not associated with

abnormal physical findings, a physical examination is not useful for diagnosis of AUC. However, it is useful for ruling out other possible diagnoses, such as upper UTI, pelvic infection,[21] or appendicitis, when symptoms are consistent with such possibilities.

If a patient reports having vaginal discharge or other suggestive symptoms, a pelvic exam should be performed to rule out vaginitis, cervicitis, or pelvic inflammatory disease.[22] Figure 3 presents an algorithm to help clinicians determine the appropriate diagnostic path.[23]

### Patient Self-Diagnosis

Women who have experienced AUC previously are usually reliable in self-diagnosis when another AUC infection occurs. In one study, 94% of patient self-diagnoses were confirmed in laboratory testing.[24] Telephone-based triage and therapy are reasonable for women with clearly identified symptoms.[23]

### Laboratory Tests

Although diagnosis of AUC is usually accomplished without laboratory testing, the diagnosis can be confirmed with certain tests.

The gold standard for identifying significant bacteriuria is the quantitative urine culture. The amount of bacterial growth required before the urine culture is considered "positive" depends on whether the patient is symptomatic. For patients without symptoms (and who are otherwise healthy), bacteriuria is considered significant when there are at least $10^5$ colony-forming units (CFU) of bacteria per mL of voided urine (also used to define asymptomatic bacteriuria). For patients with clinical symptoms suggestive of AUC, a quantitative urine culture of at least $10^2$ CFU/mL is accepted as a "positive" diagnostic criterion.[23]

Microscopic examination of urine* or a "dipstick" biochemical test are rapid tests which detect pyuria, and if positive in symptomatic women, support a diagnosis of cystitis. (*In the United States, the clinician's office should hold a Clinical Laboratory Improvement Amendment Certificate for Provider-Performed Microscopy Procedures [www.cms.hhs.gov/clia].)

A urine culture should always be obtained when the patient's history and physical suggest a complicated infection or when symptoms of high back pain or fever suggest pyelonephritis. A urine culture should be obtained for women who experience treatment failure or when a UTI recurs rapidly[20,22] (within 1 month). In addition, if a patient has had a recent UTI and/or recent antibiotic therapy for another reason, a urine culture and sensitivity should be considered.

## TREATMENT

Ideally, treatment should be initiated as soon as symptoms appear; a treatment specifically intended for AUC that targets the most common causative uropathogens would make this safe and easy to accomplish. The task for clinicians and their patients lies in balancing clinical efficacy, side effects, minimal recurrence, contained costs, and little or no chance of increasing resistance.

### Treatment Guidelines

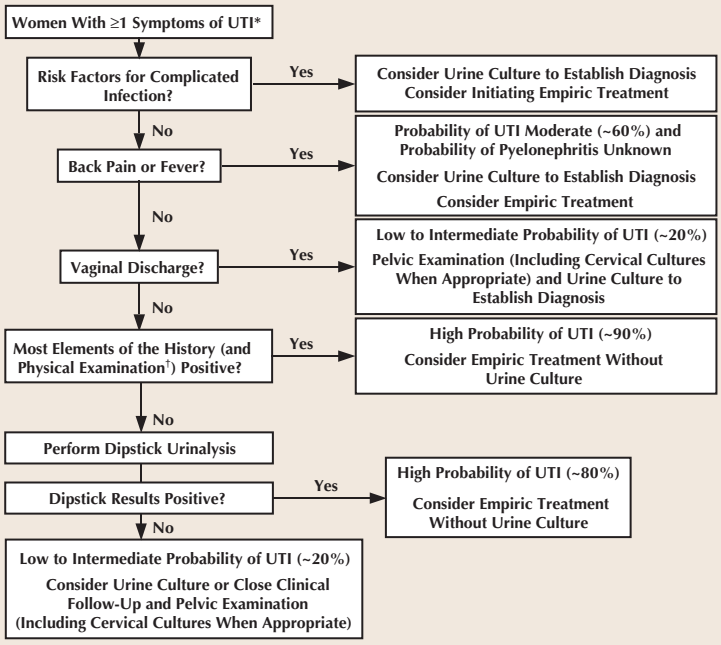
Guidelines for treatment of AUC are based on existing efficacy evidence, efforts to minimize treatment costs, and considerations of safety and patient convenience. It should always be appreciated, however, that guidelines are not rules. As resistance varies regionally, local application of guidelines for antibiotic treatment of AUC must reflect these varying resistance patterns.

The most widely used guidelines are those developed by the Infectious Diseases Society of America (IDSA). For empiric treatment of AUC, they recommend 3 days' treatment with trimethoprim/sulfamethoxazole (TMP/SMX) or TMP alone in areas where the prevalence of resistance to these drugs among *E. coli* strains causing cystitis is less than 20% (others suggest a threshold as low as 10%).[25] In areas where the prevalence of resistance to TMP/SMX exceeds this threshold, alternative agents should be considered. These include the fluoroquinolones, nitrofurantoin, and fosfomycin.

The Food and Drug Administration (FDA) recently amended its labeling regulations for empiric use of antibiotics. The new regulations, due to take effect on February 6, 2004, are aimed at reducing the development of drug-resistant bacteria by suggesting more targeted use of narrow-spectrum antibiotics to treat specific infections such as uncomplicated UTI. In addition, the FDA advises that physicians consider local susceptibility patterns when choosing therapies.[26]

**FIGURE 3**

**Diagnosis Algorithm of UTI**

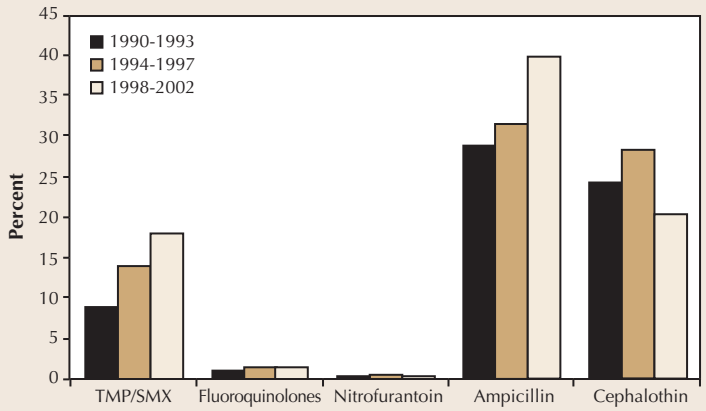



* For women with risk factors for sexually transmitted diseases, consider testing for chlamydia. The US Preventive Services Task Force recommends screening for chlamydia for all women ≤25 years of age and women of any age with >1 sexual partner, history of sexually transmitted disease, or inconsistent use of condoms.

† The only physical examination finding that increases the likelihood of any UTI is costovertebral angle tenderness, and clinicians may consider not performing this test for patients with typical symptoms of acute uncomplicated UTI (as in telephone management).

**FIGURE 4**

**_E. coli_ Resistance Has Increased**




TMP/SMX=trimethoprim/sulfamethoxazole.
Reprinted from *Infect Dis Clin North Am.*, Volume 17, Gupta K., Emerging antibiotic resistance in urinary tract pathogens. Pages 243-259, Copyright 2003, with permission from Elsevier.

## Resistance Is Increasing

Resistance of antimicrobials to *E. coli*, the pathogen usually isolated from most women with AUC, has increased (Figure 4). Of particular relevance is the increase of *E. coli* resistance to TMP/SMX, traditionally considered the first line of treatment for AUC.[27]

The fluoroquinolones are agents with efficacy comparable to that of TMP/SMX in treating AUC. *E. coli* resistance to fluoroquinolones, although increasing, is not as high as resistance to TMP/SMX in the United States.[27] Thus, fluoroquinolones seem an attractive choice for empiric treatment of AUC in areas with high resistance to TMP/SMX. However, these agents are also approved—and effective—for treating numerous other, more serious infections.[28] Therefore, the question of whether they should be reserved for more serious infections should be considered; if resistance to fluoroquinolones increases because of unnecessary overuse of these agents, their effectiveness in treating other infections will be compromised.

In an analysis of urinary isolates from laboratories in 43 states, resistance of *E. coli* to TMP/SMX was 17% and that of *S. saprophyticus* was 3% (Figure 5). These 2 pathogens remained relatively susceptible to fluoroquinolones, although resistance is increasing. Resistance was lowest for nitrofurantoin, most likely because this drug is indicated only for treatment of AUC and has an unusual, multimodal mechanism of action.[29]

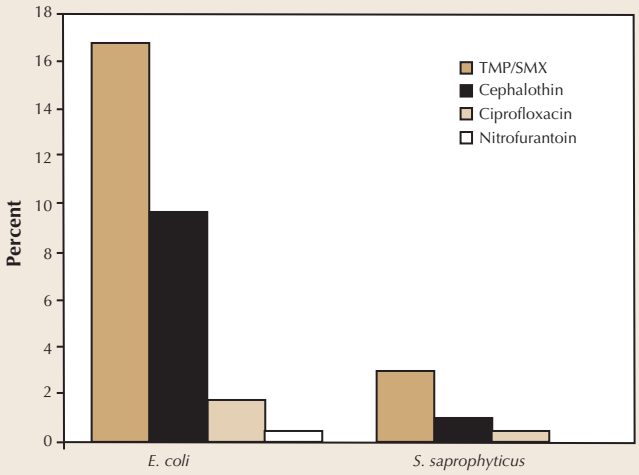
Rates of *E. coli* resistance to antibiotics vary across the United States. Figure 6 summarizes *E. coli* susceptibility to certain antibiotics in various US regions for the year 2002. The national *E. coli* susceptibility rates for 2002 were 80.2% to 80.9% for TMP/SMX, 91.2% to 93.1% for ciprofloxacin, and 96.9% to 97.2% for nitrofurantoin.[30] These numbers reflect regional trends and are used only to track regional variations. The data are derived from patients of both sexes treated in a hospital setting, and, therefore, the patients may have had more serious urinary infections. Thus, the data may overestimate resistance rates, and treatment decisions should not be based on these data alone. Many resistance data come from laboratory surveys that do not differentiate patients by sex, age, clinical syndrome, or location of treatment (eg, hospital, physician office).[31]

Unfortunately, there are few sources for clinicians to use in estimating regional resistance rates among AUC pathogens. In addition to consulting such sources as the UTI-Zone Web site (http://www. medscape.com/pages/editorial/resourcecenters/public/uti/regions/national), clinicians may also consult their own hospitals' laboratories or other regional reference laboratories, if available. In the absence of reliable local data, it is recommended that clinicians network with other treatment centers in their areas.

Resistance is also an issue of concern in countries other than the United States. Figure 7 summarizes *E. coli* resistance in isolates from urine samples from women with AUC at 240 centers in Canada and 16 countries in Europe.[32] In this analysis, resistance to TMP/SMX varies among countries and reaches very high levels in some. High rates of *E. coli* resistance to TMP/SMX have also been reported in Bangladesh (60%) and Israel (31%).[31]

**FIGURE 5**

**Resistance of Common Uropathogens to Antibiotics[29]**




## Multidrug Resistance

Multidrug resistance (MDR), resistance to 3 or more antibiotics in one strain of bacteria,[33] is being seen more and more frequently. Recent antibiotic use is one risk factor for MDR being isolated from individuals presenting to an emergency department.[34] An analysis of almost 39,000 *E. coli* urinary isolates found that 7.1% were resistant to more than one drug. Of these, 77.7% were resistant to 3 antibiotics, 20.1% to 4, and 2.2% to 5.[33]

In another study, resistance to ciprofloxacin was associated with resistance to other broad-spectrum antibiotics. Further, in this study, all *E. coli* isolates that were resistant to ciprofloxacin were reported to be TMP/SMX resistant.[33,35] Although the prevalence of MDR *E. coli* in AUC is low at this time, it may become a problem with increased use of antibiotics.[27]

## Impact of Resistance on Treatment Outcomes

Until recently, there were few studies of the association between resistance and clinical outcomes, but

evidence is now accumulating that correlates clinical failure in treatment of AUC with infection by resistant pathogens.[3]

Left untreated, approximately 50% of uncomplicated UTIs resolve spontaneously.[36] Treatment with antibiotics to which there is a high level of resistance among common uropathogens may result in lower cure rates, which is obviously less acceptable.[37] On the other hand, treatment with antibiotics to which the causative uropathogens are highly susceptible results in symptomatic improvement or cure rates of more than 85%.[36,37] Clinicians should consider using alternative, narrow-spectrum agents with high susceptibility rates for empiric treatment, especially in regions with high levels of resistance.

## TREATMENT OPTIONS

Several options are available for treating AUC in nonpregnant women, as described below and summarized in Table 1, page 6.[25,28,38-42]

### Trimethoprim/Sulfamethoxazole

TMP blocks the production of tetrahydrofolic acid by inhibiting dihydrofolate reductase. SMX competes with para-aminobenzoic acid to inhibit bacterial synthesis of dihydrofolic acid. The suggested advantage of the combination is that they inhibit 2 separate steps in bacterial biosynthesis of essential nucleic acids and proteins.[38]

TMP/SMX is currently considered the first choice for treatment of UTI,[38] and is also indicated for treatment of several other infections.[28] TMP/SMX is contraindicated for use in patients with histories of hypersensitivity reactions to sulfonamides.[28] In such cases, clinicians should consider using TMP alone or alternate therapies.

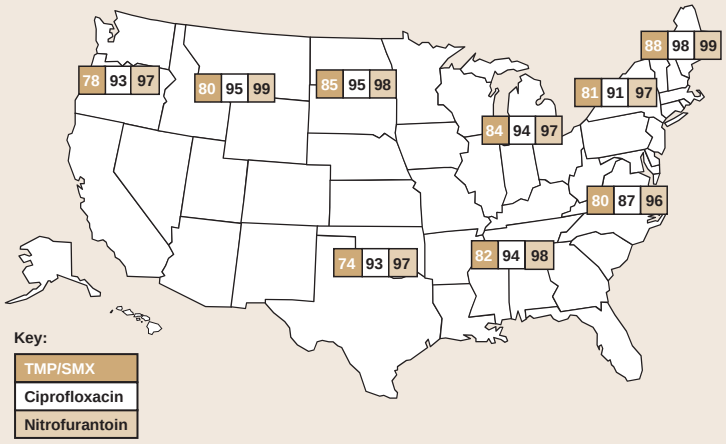
In areas with low resistance to TMP/SMX, the agent is extremely effective against most uropathogens.[25,38] However, resistance to TMP/SMX has increased. In a 6-year study of resistance among *E. coli* in urinary isolates from female outpatients in the United States, 46% of 126 institutions surveyed reported rates of resistance to TMP/SMX higher than 10%.[43] A recent review reported that *E. coli* resistance to TMP/SMX is now greater than 15% in many areas. A potential plateau has, however, recently been observed in the growth of this resistance, and it has been postulated that this may be due to decreased use of TMP/SMX for treatment of uncomplicated infections such as AUC.[27]

Two potential mechanisms of resistance to TMP/SMX have been proposed: (1) decreased permeability of the bacterial membrane and (2) production by bacteria of enzymes that bypass the inhibition by TMP/SMX of nucleic acid and protein synthesis. Although most in vitro data indicate that resistance develops more slowly with the combination than with either TMP or SMX alone, not all studies support this observation.[38]

The most common adverse effects of TMP/SMX are gastrointestinal disturbances (including nausea and vomiting) and allergic skin reactions, some of which can be quite severe. Severe reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis) have been reported but occur rarely.[44] Patients taking TMP/SMX should avoid exposure to intense sunlight because of potential photosensitivity.[28,38]

**FIGURE 6**

**Susceptibility Varies Regionally**




UTI-Zone Resource Center. Source: TSN Database-USA, ©2002, Focus Technologies, Inc. Available at www.medscape.com/pages/editorial/resourcecenters/public/uti/regions/national.

There are fewer adverse effects associated with TMP alone than with the combination. TMP/SMX should be avoided during pregnancy.[45]

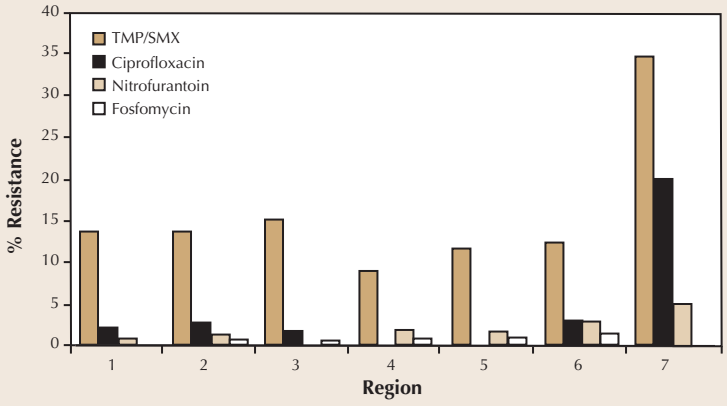
### Fluoroquinolones

Fluoroquinolones are effective against a broad array of infections and therefore are used very frequently. In addition to AUC, fluoroquinolones are used to treat pyelonephritis, complicated UTI, and chronic bacterial prostatitis.[28] The fluoroquinolones relevant to AUC are norfloxacin, ciprofloxacin, gatifloxacin, and levofloxacin. The once-daily, extended-release form of ciprofloxacin is indicated only for treating UTIs (AUC, complicated UTI, uncomplicated pyelonephritis).[46]

The fluoroquinolones inhibit bacterial topoisomerases, which are enzymes necessary for bacterial replication (eg, DNA gyrase). Fluoroquinolones achieve high urinary concentrations and are effective against many pathogens.[38]

**FIGURE 7**

***E. coli* Resistance Is a Problem in Other Countries Also[32]**




1: Austria, Germany, The Netherlands; 2: Belgium, France, Luxembourg, Switzerland; 3: Ireland, UK; 4: Denmark, Finland, Norway, Sweden; 5: Canada; 6: Greece; 7: Portugal, Spain.

The mechanism of resistance to fluoroquinolones is thought to involve a mutation in the bacterial DNA gyrase binding site and a change in the size of bacterial cell-wall porins.[38] Since the mechanisms of action of all the fluoroquinolones are similar, class resistance may be seen. That is, an organism resistant to one fluoroquinolone may be resistant to all others. The frequent use of fluoroquinolones may contribute to increasing resistance to these agents. It may be advisable to reserve this class of drugs for patients with complicated UTI, or with uncomplicated UTI and intolerance to other drugs.

The most common adverse effects of the fluoroquinolones relevant to AUC are nausea, headache, diarrhea, vaginitis, and insomnia.[28] A few studies have observed hypoglycemia in patients taking both fluoroquinolones and diabetes medication.[47] Fluoroquinolones should be avoided during pregnancy.[45]

## Nitrofurantoin

Nitrofurantoin has been indicated for treatment of acute uncomplicated UTI for more than 50 years.[9] This is its only indication.

Nitrofurantoin is converted into highly reactive metabolites by bacterial nitroreductases.[48] The metabolites inhibit bacterial ribosomal proteins at several synthetic levels, disrupting protein synthesis by bacteria. Nitrofurantoin may also exert bactericidal mechanisms at other levels.[38,48,49]

Nitrofurantoin is very active against *E. coli* and *S. saprophyticus*, the 2 most common uropathogens. It is not active against most strains of *Proteus* or *Serratia* species and has no activity against *Pseudomonas* species.[41]

Since nitrofurantoin has multiple mechanisms and sites of action, bacteria have to acquire multiple mutations to develop resistance.[27] Nitrofurantoin is urospecific, achieving high urine concentrations, but with no systemic antimicrobial activity. This may contribute to its low potential for resistance.[27,38]

**Table 1**

**Treatment Options for AUC[25,28,38-42]**

| Drug | Efficacy Against Uropathogens | Common Adverse Effects (>1%) | Approximate Cost per Day |
|---|---|---|---|
| TMP/SMX (for 3 days)* | 90%-95% against susceptible pathogens | Allergic skin reactions<br>Nausea/vomiting | $1.83 |
| Fluoroquinolones (for 3 days) | 90%-95% against susceptible pathogens | Nausea<br>Headache<br>Diarrhea<br>Insomnia | $9.10 |
| Nitrofurantoin (for 7 days) | 85%-90% against most common uropathogens | Nausea<br>Headache<br>Flatulence | $4.45 |
| Fosfomycin (single dose) | 80%-85% against *Escherichia coli* | Diarrhea<br>Headache<br>Vaginitis<br>Nausea | $35.09 |

*Off-label use.
AUC=acute uncomplicated cystitis; TMP/SMX=trimethoprim/sulfamethoxazole.

The most common adverse effects of nitrofurantoin are mild to moderate and include nausea, headache, and flatulence.[28] An acute pulmonary reaction resulting from nitrofurantoin occurs rarely, and recovery is usually rapid with cessation of treatment.[9] In a 1998 review of long-term prophylaxis for RUTI, nitrofurantoin was well tolerated,[50] and in a review of 121 million courses of nitrofurantoin treatment, low rates of major adverse reactions were observed.[9,51]

## Fosfomycin Tromethamine

Fosfomycin tromethamine has been in use for some time in other countries, and was approved in 1996 for use in the United States; like nitrofurantoin, fosfomycin is indicated only for treatment of uncomplicated UTI. However, fosfomycin is not indicated for treatment of UTI caused by *S. saprophyticus*.[40] Fosfomycin works by inactivating bacterial enopyruvyltransferase, an enzyme necessary for cell-wall synthesis.[38]

Although fosfomycin is a relatively new agent in this country, evidence to date has indicated low rates of resistance with short-term use, possibly because of its unique chemical structure.[38] Rapid emergence of resistance has been observed to occur with more than a few days' therapy.[2] It has been suggested that the potential for selection of resistant bacterial strains is reduced with single-dose therapy.[52]

The adverse effects of fosfomycin are mild and include diarrhea, headache, vaginitis, and nausea.[28]

## Treating UTI During Pregnancy

Bacteriuria, which is common in pregnancy, has been associated with significant increases in the risk for low-birthweight infants, premature delivery, preeclampsia, hypertension, anemia, and postpartum endometritis. Hence, it poses a serious threat to both mother and child. For pregnant women (as for nonpregnant women), the pathogen most commonly implicated in UTI is *E. coli*.[53] Effective treatment reduces the incidence of pyelonephritis and related complications.[45] Because of the absence of symptoms and risk for increased morbidity associated with asymptomatic bacteriuria, routine screening with urine culture should be conducted for all pregnant patients in early pregnancy.[54]

Table 2 summarizes the classification of antimicrobial agents for cystitis for use during pregnancy.[21,28,55] TMP/SMX, which is a folate antagonist, should be avoided, especially during the first trimester. The potential for exacerbation of newborn hyperbilirubinemia also limits the use of sulfonamides close to term.[45,53] Nitrofurantoin is contraindicated for use at term (38 to 42 weeks' gestation), during labor or delivery, or when onset of labor is imminent.

Of the agents listed in the table, nitrofurantoin most closely meets safety and efficacy criteria for treating bacteriuria in pregnant women. Fosfomycin is considered safe for use during pregnancy, but data on the effects of this drug in pregnancy are limited.[45]

## AUC After Menopause

Acute cystitis remains a common problem in postmenopausal women, some of whom experience frequent recurrent RUTIs. As in younger women, *E. coli* is the most common pathogen causing symptomatic AUC in healthy, postmenopausal women.[8] Several risk factors for UTI differ between pre- and postmenopausal

women. Postmenopausal women are not at risk from spermicide use, but they may have increased vaginal colonization with uropathogens due to estrogen depletion. Cystoceles are more common among postmenopausal women, as is increased postvoid residual urine volume, both of which can contribute to RUTI.[56,57]

Although systemic estrogen replacement would seem like a logical preventive measure for postmenopausal women, the recent results of the Women's Health Initiative indicate that the risks of this approach may outweigh benefits,[58] especially if preventing UTI is the only reason for prescribing systemic hormone therapy. In any case, oral estrogen supplementation has not been shown to be effective in preventing UTI.[59,60] Intravaginal estriol cream has been shown to prevent UTI, with lower systemic risk.[57] Topical estrogen use was shown in one study to increase the rate of vaginal colonization with lactobacilli and decrease the rate of colonization with Enterobacteriaceae, which may explain its ability to prevent UTI.[57] Estriol-containing vaginal pessaries are not, however, effective in preventing UTI.[61]

### Treatment Decisions

Figure 8 is a suggested algorithm for determining the appropriate treatment of nonpregnant women.[31] Healthy, nonelderly, nonpregnant women with unequivocal symptoms of AUC and no other indications of complicated infection may be assumed to have AUC without further diagnostic workup. These patients usually can be treated empirically.[31] If patients with AUC have no known allergies, have not used antibiotics—especially TMP/SMX—recently, and do not live in an area with high TMP/SMX resistance, this agent is still considered the first-line treatment. If, however, TMP/SMX is not optimal for any of the above reasons, alternatives should be considered.[31]

## PREVENTION

Efforts to prevent UTI can be pharmacologic or nonpharmacologic.

### Nonpharmacologic

Nonpharmacologic prevention of UTI entails avoiding certain behavioral risks, such as spermicide use. Postintercourse voiding has been suggested to be protective, but has not been confirmed in large studies.[13]

Several studies have suggested a moderate benefit of drinking cranberry juice in decreasing the risk of UTI.[14,62,63] Patients should be aware that evidence for benefit remains inconclusive and that large volumes of the juice can add to their daily calorie and sugar intake. The consumption of a lactobacillus drink has not been shown to be effective in the treatment of AUC.[63]

### Pharmacologic

Immunizing vaccines are being developed, but clinical trials to date have not been encouraging.

Pharmacologic management of RUTIs includes 3 options: continuous low doses of an antibiotic for women who have frequent RUTIs, postcoital prophylaxis for patients whose infection onset seems to be associated with intercourse, and patient self-diagnosis and treatment initiation. TMP/SMX, a fluoroquinolone, or nitrofurantoin may be used for prophylactic treatment.[12] Fosfomycin is not recommended as resistance may emerge quickly.[2]

Although patient self-diagnosis and treatment initiation are not considered prevention, such early treatment can help shorten the course of infection. As mentioned,

**TABLE 2**

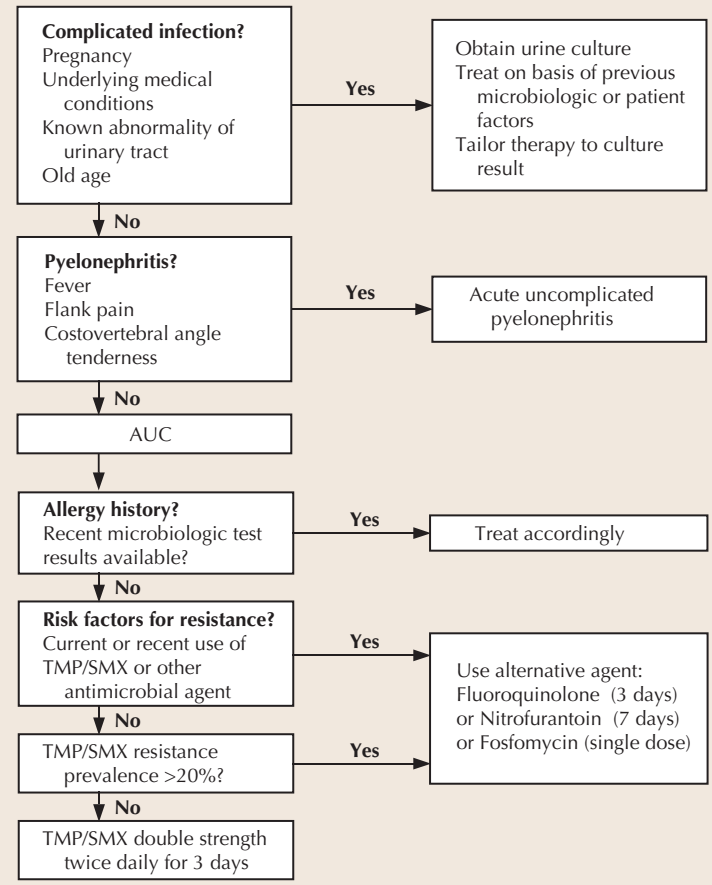
**Treating UTI During Pregnancy** [21,28,55]

| Drug | Use in Pregnancy |
|---|---|
| TMP/SMX | C,* D at term |
| Fluoroquinolones | C |
| Nitrofurantoin | B† |
| Fosfomycin | B |

UTI=urinary tract infection.
*B: Animal studies do not demonstrate or human studies do not confirm fetal risk.*
*C: Animal studies indicate adverse fetal effects not refuted adequately in human studies.*
*D: Positive evidence exists of human fetal risk.*
* May cause folate deficiency. Also contraindicated for use at term.
† Not to be used close to or during labor and delivery (may cause hemolytic anemia in newborns).

**FIGURE 8**

**Treatment Algorithm**




Adapted with permission from Gupta K, et al. *Ann Intern Med.* 2001;135:41-50.

women who experience RUTI are usually skilled at self-diagnosis based on symptoms. Several studies have supported the efficacy and cost-effectiveness of this method, with self-diagnostic accuracy as high as 94% and treatment response of 92%.[24] This method compared favorably with ongoing antibiotic prophylaxis[64] and patients expressed satisfaction with the outcome and were comfortable with its use.[24]

## CONCLUSIONS

From the patient's and clinician's perspective, prompt symptom resolution is usually the most important goal of treatment. From a public health standpoint, a major objective of treatment planning is containing the spread of bacterial resistance to antibiotics, so that potent, broad-spectrum antibiotics will remain effective for treating serious infections. To accomplish the combined patient and community goals, whenever possible, clinicians should reserve broad-spectrum antibiotics for more serious infections requiring therapy with these drugs. For AUC, treatment with urospecific agents that target the most common uropathogens should be considered.

Guidelines for empiric treatment will continue to change as antimicrobial resistance evolves. Although TMP/SMX is currently a recommended first-line therapy for AUC, increasing resistance requires continuing reassessment and consideration of alternatives. The efficacy of the fluoroquinolones in treating serious infections should be preserved if possible; one way to do this is to refrain from using them to treat infections for which narrower-spectrum drugs are effective.

It is important for clinicians to be aware of resistance rates in their particular regions of the country, and to choose therapies that have low rates of resistance and are not likely to increase resistance or cross-resistance.

Finally, clinicians should ensure that both they and their patients are sufficiently educated regarding the appropriate use of antibiotics—when they should be used at all, and which ones for a given clinical situation. Both individual patients and the broader community will benefit from this awareness.

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# MANAGING ACUTE UNCOMPLICATED CYSTITIS IN WOMEN IN THE ERA OF ANTIBIOTIC RESISTANCE

## CME Credit Information and Posttest Assessment

For primary care physicians (family physicians, general practitioners, internal medicine physicians), obstetrician/gynecologists, nurse practitioners, physician assistants, nurse midwives, and other healthcare professionals who care for patients with acute uncomplicated cystitis.

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This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Minnesota and IMED Communications. The University of Minnesota is accredited by the ACCME to provide continuing medical education for physicians.

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Approved by the Continuing Education Approval Program of the National Association of Nurse Practitioners in Women's Health for 1 contact hour, including 1 hour of pharmacology. Offering number 03-51.

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**INSTRUCTIONS:**

To apply for category 1 credit, you must:

- Complete the posttest and evaluation form
- Mail/fax your completed form to:

Managing AUC in Women
University of Minnesota
Office of Continuing Medical Education
200 Oak Street SE, Suite 190
Minneapolis, MN 55455
OR fax to 612-626-7766

## POSTTEST Please circle the correct answer.

1. Which of the following does *not* identify a UTI as complicated?
   a. Patient has an indwelling catheter
   b. Patient has multiple sex partners
   c. Patient is pregnant
   d. Patient has diabetes
   e. None of the above

2. Patients with RUTIs can often self-diagnose and initiate treatment on their own.
   a. True b. False

3. By 32 years of age, _____% of women will have had at least one UTI.
   a. 10 d. 70
   b. 20 e. 90
   c. 50

4. *E. coli* is the causative pathogen in ____% of AUC cases.
   a. >97 d. 20 to 30
   b. 80 to 85 e. <10
   c. ~50

5. Women with family histories of UTI are no more likely to have UTIs than are women without family histories of UTI.
   a. True b. False

6. Recent antibiotic use predisposes a women to have a:
   a. UTI
   b. UTI caused by a TMP/SMX-resistant pathogen
   c. Both of the above
   d. Neither of the above

7. The highest *E. coli* resistance levels seen in the United States are to:
   a. TMP/SMX
   b. Ciprofloxacin
   c. Nitrofurantoin
   d. Fosfomycin

8. In symptomatic women with acute uncomplicated cystitis, bacteriuria is considered significant when urinalysis reveals bacteria levels at least _____ CFUs/mL of urine.
   a. $10^2$ c. $10^4$
   b. $10^3$ d. $10^5$

9. Antibiotics considered safe for use during pregnancy are:
   a. TMP/SMX and fluoroquinolones
   b. TMP/SMX and nitrofurantoin
   c. Fluoroquinolones and fosfomycin
   d. Nitrofurantoin and fosfomycin
   e. Fluoroquinolones and nitrofurantoin

10. Prophylaxis against UTI can be performed using:
    a. TMP/SMX, nitrofurantoin, or fosfomycin
    b. A fluoroquinolone, nitrofurantoin, or fosfomycin
    c. TMP/SMX, a fluoroquinolone, or nitrofurantoin
    d. TMP/SMX, a fluoroquinolone, or fosfomycin

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# Managing Acute Uncomplicated Cystitis in Women in the Era of Antibiotic Resistance

**Vol. 5 No. 9**

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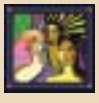

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