

# CLINICIAN®

Vol. 21 No. 1

ISSN 0264-6404

June 2003

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



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

National Association of Managed Care Physicians



American College of Nurse-Midwives

National Association of Nurse Practitioners in Women's Health



The Society for Women's Health Research



JOINTLY SPONSORED BY



AND



UNIVERSITY OF WASHINGTON  
SCHOOL OF MEDICINE

IMED  
Communications LLC

This program is supported by an educational grant from Procter & Gamble Pharmaceuticals, Inc. **P&G**

## Target Audience

Urologists, obstetrician/gynecologists, pediatricians, primary care physicians (general practitioners, family practitioners, internal medicine physicians), and other healthcare professionals who care for patients with acute uncomplicated cystitis

## Learning Objectives

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

- Discuss the etiology of acute cystitis
- Describe the impact of the increase in antimicrobial resistance on the management of acute cystitis
- Describe the risk factors that influence the development and recurrence of acute cystitis in at-risk populations
- Identify the benefits and disadvantages of both traditional and newer antimicrobial agents
- Review the latest pharmacologic/nonpharmacologic strategies for prevention
- Identify strategies for managing special patient populations (eg, pediatric, pregnant, the older woman)

## Needs Assessment

Urinary tract infections (UTIs) are among the most common infections in women and, as such, account for significant morbidity and healthcare utilization. In the United States, UTIs account for more than 7 million office visits and more than 1 million hospitalizations each year. Specific populations at increased risk of acute cystitis or of significant morbidity from UTI include children, pregnant women, and the older woman. The predominant uropathogens have generally remained constant over the past decade; however, for the most common pathogens, such as *Escherichia coli* and *Staphylococcus saprophyticus*, there have been important changes in resistance patterns to commonly used antimicrobial agents. Rates of resistance are increasing faster than new antimicrobial agents can be developed. In addition, the inappropriate use of antimicrobial agents in acute cystitis can lead to increased resistance levels in pathogens, causing more serious infections and making these antimicrobials ineffective when needed most.

## Faculty Disclosure Information

The University of Washington School of Medicine endorses the standards of the Accreditation Council for Continuing Medical Education and the guidelines of the Association of American Colleges that the sponsors of continuing medical education activities and the speakers at these activities disclose significant relationships with commercial companies whose products or services are discussed in educational presentations. For speakers, significant relationships include receiving from a commercial company research grants, consultancies, honoraria and travel, or other benefits, or having a self-managed equity interest in a company. Disclosure of a relationship is not intended to suggest or condone bias in any presentation but is made to provide participants with information that might be of potential importance to their evaluation of a presentation.

## Faculty Disclosures

Faculty Member	Affiliation/Financial Interest						
	Grants/Research Support	Consultant	Speaker's Bureau	Stock Shareholder	Honorarium	Other Financial or Material Support	No Financial Interest or Affiliation
J. Fourcroy, MD, PhD, MPH		Depomed					
K. Gupta, MD, MPH	Bayer, Ortho-McNeil, Procter & Gamble	Bayer	Bayer				
T. Hooton, MD	MedImmune	Bayer, Procter & Gamble	Bayer		Bayer, Bristol-Myers Squibb, Ortho-McNeil		
J. Johnson, MD	Bayer, Merck, Ortho-McNeil						
J. Krieger, MD							✓
M. Martens, MD		Merck, Sharpe & Dohme	Procter & Gamble				
A. Moore, RNC, MSN, CNP			Ortho-McNeil, Pharmacia, Wyeth				
L. Nicolle, MD	Bayer, GlaxoSmithKline, MedImmune	Leo Pharmaceuticals			Bayer, Leo Pharmaceuticals		
A. Ronald, MD							✓
T. Schlager, MD							✓
R. Sheeler, MD		Procter & Gamble					
A. Stapleton, MD							✓

## Product Disclosure Information

When an unlabeled use of a commercial product, or an investigational use not yet approved, is discussed during an educational activity, the accredited provider shall require the presenter to disclose the Food and Drug Administration status to the participants. This monograph may include discussion of unapproved/investigational or unlabeled uses of commercial products.

**Product**  
All UTI therapies

**Off-Label Use**  
Prophylaxis

# Managing Acute Uncomplicated Cystitis in the Era of Antibiotic Resistance

## PROGRAM CHAIR

**Lindsay E. Nicolle, MD, FRCPC**

Professor  
Department of Internal Medicine  
University of Manitoba  
Winnipeg, Manitoba, Canada

## CME PLANNING/STEERING COMMITTEE

**Thomas M. Hooton, MD**

Professor of Medicine  
Department of Medicine  
University of Washington  
School of Medicine  
Seattle, Washington

**Wanda K. Jones, DrPH**

Deputy Assistant Secretary  
for Health  
Office on Women's Health  
Department of Health  
and Human Services  
Washington, DC

**Lindsay E. Nicolle, MD, FRCPC**

Professor  
Department of Internal Medicine  
University of Manitoba  
Winnipeg, Manitoba, Canada

**Sandy Pomerinke**

Program Coordinator  
University of Washington  
School of Medicine  
Seattle, Washington

## FACULTY

**Jean L. Fourcroy, MD, PhD, MPH**

Assistant Professor  
Department of Surgery  
Uniformed Services  
University of Health Sciences  
Bethesda, Maryland

**James R. Johnson, MD**

Professor of Medicine  
Department of Medicine  
University of Minnesota  
VA Medical Center  
Minneapolis, Minnesota

**Anne Moore, RNC, MSN, CNP**

Professor of Nursing  
Women's Health Nurse Practitioner  
Vanderbilt University  
Nashville, Tennessee

**Theresa A. Schlager, MD**

Associate Professor of Pediatric  
Infectious Disease  
Department of Emergency Medicine  
Charlottesville, Virginia

**Kalpana Gupta, MD, MPH**

Acting Assistant  
Professor of Medicine  
Department of Medicine  
University of Washington  
School of Medicine  
Seattle, Washington

**John N. Krieger, MD**

Professor  
Department of Urology  
University of Washington  
School of Medicine  
VA Puget Sound Urology  
Seattle, Washington

**Lindsay E. Nicolle, MD, FRCPC**

Professor  
Department of Internal Medicine  
University of Manitoba  
Winnipeg, Manitoba, Canada

**Robert D. Sheeler, MD**

Consultant in Family Medicine  
Mayo Clinic  
Rochester, Minnesota

**Thomas M. Hooton, MD**

Professor of Medicine  
Department of Medicine  
University of Washington  
School of Medicine  
Seattle, Washington

**Mark G. Martens, MD, FACOG**

Professor and Vice-Chairman  
Department of Obstetrics  
and Gynecology  
University of Oklahoma-Tulsa  
Tulsa, Oklahoma

**Allan Ronald, MD, FRCPC**

Emeritus Professor  
University of Manitoba  
Faculty of Medicine  
St. Boniface Hospital  
Winnipeg, Manitoba, Canada

**Ann E. Stapleton, MD**

Associate Professor  
Department of Medicine  
University of Washington  
School of Medicine  
Seattle, Washington

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 Washington School of Medicine and IMED Communications. The University of Washington School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

The University of Washington School of Medicine designates this educational activity for a maximum of 2.5 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

**Release Date: June 2003**

**Term of Approval: June 2005**

# TABLE OF CONTENTS

# PAGE

<b>Target Audience</b> .....	Inside Front Cover
<b>Learning Objectives</b> .....	Inside Front Cover
<b>Needs Assessment</b> .....	Inside Front Cover
<b>Faculty Disclosure Information</b> .....	Inside Front Cover
<b>Faculty Disclosure</b> .....	Inside Front Cover
<b>Product Disclosure Information</b> .....	Inside Front Cover
<b>Faculty</b> .....	i
<b>Introduction</b> .....	1
<b>The Spectrum of UTIs</b> .....	1
<b>Epidemiology of UTI</b> .....	2
Risk Factors .....	2
Changes With Age .....	3
Pregnancy .....	3
Costs and Consequences .....	3
<b>Etiology of UTI</b> .....	3
Host Factors and Special Populations .....	4
Pathogenesis .....	4
<b>Differential Diagnosis</b> .....	4
History .....	4
Physical Examination .....	4
Laboratory Testing .....	4
Optimizing Diagnostic Measures .....	5
<b>The Challenge of Antimicrobial Resistance in Treating AUC</b> .....	6
Emerging Resistance in Uropathogens .....	7
Regional Variation in Resistance .....	7
Resistance Trends in Other Countries .....	8
Multiple-Drug Resistance .....	8
Clinical Effects of Resistance .....	9
<b>Optimal Treatment for AUC</b> .....	10
Considerations in Antibiotic Selection .....	11
Antibiotic Options .....	11
Clinical and Bacteriologic Response .....	12
<b>Prevention of RUTI</b> .....	12
<b>Treating UTI in Special Populations</b> .....	13
Infants and Children .....	14
Pregnant Women .....	14
Elderly Patients .....	14
<b>Managed Care Considerations</b> .....	14
<b>Conclusions</b> .....	15
<b>References</b> .....	15
<b>Posttest</b> .....	17

## INTRODUCTION

Acute uncomplicated cystitis (AUC) is a common problem for women, and several management issues remain unresolved.

- Patients with recurrent AUC, especially those with frequent recurrence, have impaired quality of life, including time lost from work, school, and other activities. Because many women have frequent recurrent urinary tract infections (RUTIs), AUC may pose a considerable burden to the individual patient and a heavy social burden in terms of medical resources used and productivity lost.
- Recommendations for management of AUC have generally included empiric therapy based on history, sometimes with rapid urine testing. Several antimicrobial agents are effective, but recommended agents and regimens continue to evolve. Increasing antimicrobial resistance levels observed in urinary pathogens have been a major impetus for changes in empiric therapy. When the infecting organism is resistant, the incidence of treatment failure and recurrent infection is increased, with associated human and economic costs.
- Widespread empiric antimicrobial use is a concern in the context of promoting resistance. Broad-spectrum antimicrobials effective in treating AUC in an individual patient may induce resistance in pathogens that cause more serious or even life-threatening infections. Resistant pathogens pose a threat not only to the original patient but also to the community, by the transmission of resistant organisms or genetic resistance elements. Resistance has limited the effectiveness of penicillins, cephalosporins, trimethoprim-sulfamethoxazole (TMP/SMX), and some macrolides and is beginning to be observed with fluoroquinolones for some important pathogens, such as *Streptococcus pneumoniae*.

Where possible, a more targeted approach, using drugs indicated only for AUC, seems desirable.

The emergence of resistance has an even greater impact on patients with UTIs other than AUC. Management of UTIs in patients with comorbidities, in children, in pregnant women, and in the elderly, including institutionalized patients, must also address concerns regarding antimicrobial resistance.

This monograph discusses treatment approaches for AUC in the current era of antibiotic resistance. It is based in part on the proceedings of a scientific roundtable held in Seattle, Washington, and jointly sponsored by the University of Washington School of Medicine and IMED Communications with the support of an educational grant from Procter & Gamble Pharmaceuticals, Inc.

## The Spectrum of UTIs

The problem of UTI encompasses a wide range of patient populations, infecting organisms, degrees of severity, and levels of infection in the genitourinary tract. Any discussion of the epidemiology, etiology, diagnosis, and treatment of AUC must consider the wide spectrum of UTIs. This includes:

### Complicated versus uncomplicated UTI.

Complicated UTI is defined as infection in a patient with structural or functional abnormalities of the genitourinary tract, whereas uncomplicated UTI is infection in a patient without such abnormalities. These abnormalities may include presence of urinary calculi, cystic renal disease, obstruction, anatomic abnormalities, neurologic bladder dysfunction, or a foreign body. UTIs in patients with transplanted kidneys and metabolic or immunologic illnesses are also considered complicated.<sup>1</sup>

The distinction between uncomplicated and complicated UTIs has important implications for all phases of management, including pre- and post-treatment evaluation, selection of antimicrobial, and duration of treatment. Factors that should raise the clinician's suspicion of complicated UTI are listed in Table 1.<sup>2</sup>

**Table 1**

### Factors Suggestive of Complicated Urinary Tract Infection (UTI)

Male sex	Functional or anatomic abnormality of urinary tract
Advanced age	Childhood UTI
Presentation in an urban emergency department	Recent antimicrobial use
Hospital-acquired infection	Symptoms for >7 days
Pregnancy	Diabetes
Indwelling urinary catheter	Immunosuppression
Recent urinary tract instrumentation	

Adapted from *Infect Dis Clin North Am*, Vol. 1, Johnson JR, Stamm WE, Diagnosis and treatment of acute urinary tract infections, 783, Copyright 1987, with permission from Elsevier.

**RUTI.** RUTIs are either *relapses* or *reinfections*. A relapse is a recurrent infection with a posttherapy organism identical to the pretherapy isolate. In women, relapses usually occur within 14 days after completion of treatment; in men, the interval may be much longer because of persistent infection in the prostate. Reinfection is defined as infection with a new organism.<sup>1</sup>

**Pyelonephritis.** Pyelonephritis is infection of the kidney. It is usually an acute infection process.<sup>3</sup>

**Urethritis, acute urethral syndrome.** Urethral inflammation may present as dysuria, even when the urine is sterile. This condition is often due to sexually transmitted disease and is more likely to be identified in women with new partners. It is associated with sexually transmitted bacterial or viral pathogens, such as *Chlamydia trachomatis* or *Neisseria gonorrhoeae*, rather than with the common urinary pathogens.<sup>3</sup>

**Asymptomatic bacteriuria (ASB).** ASB is bacteria in the urine without clinical symptoms. ASB is common and benign in most patients; however, pregnant women and patients undergoing instrumentation with untreated ASB may experience significant adverse effects because of the ASB; treatment is indicated for these patients.<sup>1</sup>

### Epidemiology of UTI

AUC is the most common bacterial infection. It is primarily a disease of young, sexually active women and uncommon in men. About 1 in 3 women will have at least 1 diagnosed UTI necessitating

antibiotic treatment by age 24, and 40% to 50% of women will have at least 1 UTI over their lifetimes.<sup>4</sup> The 1997 National Health Care Survey reported 2.7 million visits to ambulatory care settings for cystitis and other bladder disorders and 8.3 million visits for UTIs at unspecified sites (International Classification of Diseases classifications).<sup>5</sup>

Several studies report UTI rates in women. In 800 sexually active young women seeking contraception at a university health clinic or a health maintenance organization (HMO), the incidence was 70 UTIs per 100 person-years for the university women and 50 per 100 person-years for the HMO cohort.<sup>6</sup> A telephone survey based on random-digit dialing obtained information from approximately 2000 women. Of those more than 18 years of age, 10.8% reported at least 1 presumed UTI during the past 12 months. The highest percentage of incidence (17.5%) was reported by women 18 to 24 years of age. Most of the women in any age group who reported a UTI in the last year also reported 2 or more episodes in their lives. The incidence in this survey suggests that 11.3 million women in the United States experienced UTI in 1995.<sup>7</sup>

Figure 1 shows age-specific UTI incidence. The highest incidence is for those 18 to 24 years of age, but no age cohort has an incidence far below 10%.<sup>7</sup>

### Risk Factors

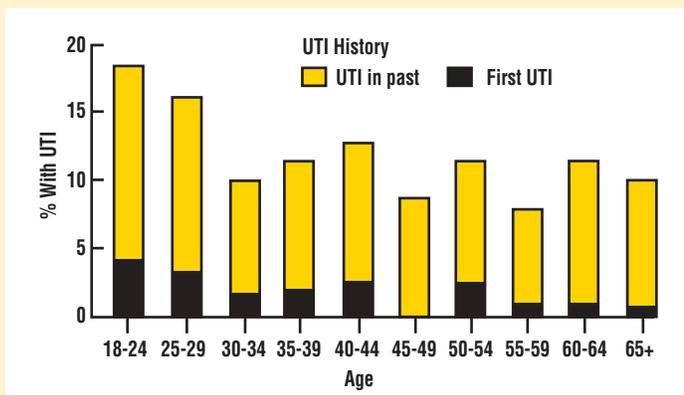
Table 2 lists recognized risk factors for UTI in young women.<sup>6, 8-13</sup> There is a strong association with sexual activity. In college-age women, UTIs almost invariably are reported following recent sexual activity. In one study, all women with infections had engaged in sexual intercourse during the preceding 4 weeks compared with less than half of noninfected controls. In another study, only 1.2% of women with first-time UTIs reported that they had not been sexually active in the preceding 2 weeks, compared with 24.7% of controls. In addition, 50% of women with first-time UTIs and only 39% of controls reported intercourse 3 or more times per week. Of women with RUTIs, 58% had had intercourse 3 or more times per week.<sup>9,10</sup>

There is an association between contraceptive method and the risk of acquiring a UTI. The primary risk factor is the use of spermicide. Diaphragms, which pose a small increase in risk themselves, are almost always used with spermicide. In one study, the use of a diaphragm and spermicide increased the UTI risk from 1.9 for women who had used this contraceptive method once in the previous week to 14.1 for those who had used it 4 times.<sup>6</sup>

Spermicides may increase the risk of UTI by suppressing the growth of hydrogen peroxide-producing lactobacilli in the vagina, reducing

**Figure 1**

**Survey-Based Incidence of Urinary Tract Infection (UTI) During Previous Year in Women by Age and History**



Reprinted from *Ann Epidemiol*, Vol. 10, Foxman B, et al. Urinary tract infection: self-reported incidence and associated costs, 512, Copyright 2000, with permission from Elsevier.

**Table 2**

**Most Common Risk Factors for UTI<sup>6,8-13</sup>**

Physical	Behavioral
Congenital abnormalities	Frequent sexual intercourse
Urinary obstruction	New or multiple sexual partners
Estrogen deficiency	Diaphragm use
Urogenital surgery	Spermicide use
Diabetes	Recent antibiotic use
	Consumption of carbonated beverages

resistance to bacterial colonization.<sup>6,9</sup> The use of spermicide-coated condoms increases the risk of UTI substantially over that of using condoms without spermicide.<sup>12</sup>

A new sexual partner nearly doubles the risk of acquiring a UTI.<sup>8</sup> Recent antibiotic use also increases the risk.<sup>14</sup> A number of other host behaviors that have been suggested as potential risk factors are not linked to UTI. These include the type of menstrual protection, voiding habits, diet, postmicturition wiping habits, and type of clothing worn.<sup>8</sup>

### Changes With Age

In the first year of life, UTI is more common in boys than in girls. Approximately 2.7% of boys have UTIs by the time they are 1 year of age. The incidence among boys then decreases to a range of 0.03% to 1.2% during school years. In girls, the incidence of UTI is about 0.7% in the first year of life, increasing to 1% to 3% during the school years.<sup>15</sup>

ASB is much more common in women than in men throughout life. The prevalence of bacteriuria increases in females by about 1% per decade and reaches 8% to 10% in elderly women.<sup>16</sup> Uncomplicated UTIs are uncommon in males, and bacteriuria in men suggests complicated infection.<sup>17</sup>

Among otherwise healthy, noninstitutionalized elderly persons, genitourinary tract infections are the second most common infections after those of the respiratory tract, accounting for 24% of identified infections in a small, prospective study.<sup>15</sup> UTI in postmenopausal women is associated with premenopausal UTIs and nonsecretor status, as well as with cystoceles, previous genitourinary surgery, and increased postvoid residual urine.<sup>13</sup>

Institutionalized elderly people are more likely to have indwelling catheters, urologic functional or anatomic abnormalities, or other comorbidities affecting UTI than are their independently living counterparts. The prevalence of ASB is also greater. Despite the high prevalence of ASB, there is no evidence that it is harmful to this population.<sup>4,15</sup>

### Pregnancy

The prevalence of ASB in pregnant women has been reported to vary from 4% to 11% and is usually thought to be 4% to 7%. This is similar to the prevalence in nonpregnant women, suggesting that pregnancy is not a risk factor for bacteriuria.<sup>18</sup> Between 1% and 4% of women will experience first episodes of AUC during pregnancy. In addition, 1% to 2% will develop acute pyelonephritis, usually around the end of the second or beginning of the third trimester.<sup>4,19</sup>

Most women with ASB in pregnancy are identified in the early prenatal period. Only a small percentage,

1% to 2%, acquire bacteriuria later in pregnancy. From 20% to 40% of pregnant women with untreated ASB will develop pyelonephritis later in pregnancy.<sup>20</sup> Physiologic and anatomic changes to the urinary tract during pregnancy favor urine stasis and reflux, leading to symptomatic infection.<sup>4,19</sup>

Acute pyelonephritis is dangerous in later pregnancy, as it may precipitate premature labor. ASB and symptomatic UTI have also been associated with intrauterine growth retardation and low birth weight. The rate of fetal mortality was found to be 2.4 times higher for women with UTIs than for controls from the same geographic area.<sup>19</sup>

### Costs and Consequences

Although the costs of treating a single case of AUC are moderate, the large number of cases treated annually makes overall costs considerable. Direct costs of treatment for the 11.3 million cases of UTI requiring prescriptions in 1995 were estimated at \$474 million in medical expenses, \$185 million in treatment-related nonmedical expenses, and \$936 million in indirect costs—a total of \$1.6 billion annually.<sup>7</sup>

AUC is not a trivial problem for women who experience it. An episode of uncomplicated UTI in college women resulted in an average of 6.1 days with symptoms, 2.4 days of restricted activity, 1 day of time lost from work or classes, and 0.4 days of bedrest. Within 3 to 4 months of a first UTI, 20% to 30% of women will experience RUTI with attendant short-term morbidity.<sup>11</sup>

### Etiology of UTI

The principal pathogen for AUC is *Escherichia coli*, which is responsible for 80% to 90% of infections. Of the remaining pathogens, *Staphylococcus saprophyticus*, isolated from 10% to 15%, is the most common organism (Table 3).<sup>21,22</sup> Other pathogens are infrequent.

**Table 3**

#### Most Frequent Urinary Pathogens

Uncomplicated UTI	Complicated UTI
<i>Escherichia coli</i>	<i>E coli</i>
<i>Staphylococcus saprophyticus</i>	<i>Klebsiella</i> spp
<i>Klebsiella</i> spp	<i>Enterobacter cloacae</i>
<i>Proteus mirabilis</i>	<i>Serratia marcescens</i>
Group B streptococci	<i>P mirabilis</i>
	<i>Pseudomonas aeruginosa</i>
	<i>Enterococcus faecalis</i>
	Group B streptococci

Adapted from *Am J Med*, Vol. 113 (suppl 1A), Ronald A, The etiology of urinary tract infection: traditional and emerging pathogens, 14S, Copyright 2002, with permission from Excerpta Medica.

There is a wider variety of organisms isolated from complicated UTIs. The difference in microbiology between complicated and uncomplicated UTI has major implications for diagnosis and treatment: If symptoms and history point to uncomplicated infection, empiric treatment with an antimicrobial that is effective against the pathogens that cause more than 90% of infections is rational and justified. When a complicated UTI is suspected, it is important to identify the specific pathogen and tailor the treatment accordingly.

### *Host Factors and Special Populations*

In children with uncomplicated infection, the most common pathogens are the Enterobacteriaceae, primarily *E coli*.<sup>23</sup> Children with comorbidities are more likely to be infected by pathogens rarely isolated from healthy children. Complicated UTI also occurs in children, in association with abnormalities, such as renal calculi and vesicoureteral reflux, that cause urinary stasis.<sup>23</sup> Nosocomial infections are strongly associated with urethral instrumentation. The most likely pathogens include *E coli* (28%) and *Candida* spp (18%); fungi are becoming increasingly common uropathogens in nosocomial infections. *Pseudomonas aeruginosa* may be isolated from up to 10% of nosocomial UTIs in children.<sup>22</sup>

*E coli* is the most frequent uropathogen in elderly patients. *S saprophyticus* is rare in these patients, although other gram-positive pathogens, such as *Enterococcus* spp, are common, accounting for 10% to 20% of infections.<sup>22</sup> Polymicrobial infection occurs in 10% to 25% of institutionalized elderly patients.<sup>24</sup> Because of the frequent use of systemic antibiotics in the institutionalized elderly, resistant gram-negative rods such as *P aeruginosa* and *Providencia* spp are common.<sup>22,24</sup>

### *Pathogenesis*

The initial step in the pathogenesis of UTIs caused by *E coli* is the colonization of the urinary tract or vaginal introitus by potential pathogens. Colonizing organisms usually originate in the normal gut flora. Women are probably at greater risk for AUC than are men because of the much shorter female urethra.<sup>22,25</sup>

Uropathogenic strains of *E coli* are characterized by filaments called fimbriae, or pili, that carry adhesion molecules at their tips. These interact directly with host cell-surface receptors, facilitating attachment to the bladder uroepithelium and, perhaps, facilitating internalization of bacteria into epithelial cells. Women with RUTI have much higher numbers of *E coli* adhering to epithelial cells than do women with isolated infections.<sup>22</sup>

### **Differential Diagnosis**

In many cases, a diagnosis of AUC can be made with confidence based on history alone.

Confirmatory information available through rapid urine tests includes identification of leukocytes in the urine (pyuria) or urine nitrites secondary to bacterial metabolism. The history should include identification of any features that may suggest complicated UTI.

### *History*

The presenting symptoms of AUC are caused by inflammation of the bladder and urethra, leading to the most prominent symptoms: dysuria, urgency, and frequency. There also may be nocturia, voiding of small volumes, new or increased incontinence, and suprapubic pain. Some patients develop gross hematuria or notice cloudy and malodorous urine.<sup>2</sup>

The differential diagnosis includes other syndromes that may cause dysuria. For young women, the most common is vaginitis or urethritis caused by sexually transmitted pathogens. Table 4 summarizes the most important diagnostic differences between the major infectious causes of acute dysuria in women.<sup>21</sup>

Some patients may distinguish between internal dysuria, where the discomfort or pain seems to be in the urethra and begins before the initiation of voiding, and external dysuria, where the discomfort is localized to the perineum and is not felt until after voiding has begun and mucosal surfaces are irritated by the urine. Internal dysuria suggests inflammation of the urethra or bladder, and external dysuria indicates vaginitis or inflammation of the vulva (eg, trichomoniasis, yeast infection, bacterial vaginosis).<sup>2</sup>

If the patient has a new sex partner or vaginal discharge, a sexually transmitted disease, such as vaginitis, cervicitis, or urethritis, must be considered. Voiding symptoms, such as frequency, urgency, and voiding small volumes, are less common in urethritis than in AUC and rare in vaginitis. Gross hematuria, present in about half of women with AUC, and suprapubic pain or tenderness are both rarely found in combination with dysuria except in AUC.<sup>2</sup>

### *Physical Examination*

A physical examination is not helpful in confirming a diagnosis of AUC because there are no consistent, specific findings. The examination may be helpful, however, in identifying other disorders. Suprapubic tenderness may be found in AUC, but fever and/or flank pain in a patient with voiding symptoms suggests renal infection. A pelvic examination may confirm vaginitis, cervicitis, vulvar infection, or pelvic inflammatory disease.<sup>2</sup>

### *Laboratory Testing*

Confirming a UTI requires documentation of the presence of bacteria in bladder urine.

**Table 4****Major Infectious Causes of Acute Dysuria in Women****Laboratory Analysis**

Condition	Pathogen	Pyuria	Hematuria	Urine Culture	Symptoms/Signs/Factors
Cystitis	<i>E coli</i> , <i>S saprophyticus</i> , <i>Proteus</i> spp, <i>Klebsiella</i> spp	Usually	Sometimes	≥10 <sup>2</sup>	Abrupt onset, relatively severe symptoms: dysuria, frequency/urgency, suprapubic/low-back pain or tenderness
Urethritis	<i>Chlamydia trachomatis</i> , <i>Neisseria gonorrhoeae</i> , herpes simplex virus	Usually	Rarely	<10 <sup>2</sup>	Gradual onset, mild symptoms: vaginal discharge/bleeding, new sexual partner, abdominal pain, external lesions
Vaginitis	<i>Candida</i> spp <i>Trichomonas vaginalis</i>	Rarely	Rarely	<10 <sup>2</sup>	Vaginal discharge/odor, pruritus, dyspareunia, vulvovaginitis on exam, external dysuria

Adapted with permission from Stamm WE, Hooton TM, *N Engl J Med*. 1993;329:1328-1334. Copyright 1993 Massachusetts Medical Society. All rights reserved.

Contamination (a bacterial source other than bladder urine) must be differentiated from infection (bacteria from bladder urine). The traditional level of bacteriuria defining UTI is 10<sup>5</sup> colony-forming units (CFU)/mL of urine; however, recent studies have shown that this standard is insufficiently sensitive in acutely symptomatic women. One third to one half of cases of AUC have bacterial concentrations <10<sup>2</sup> CFU/mL. Defining infection as ≥10<sup>2</sup> CFU/mL has the best combination of sensitivity (95%) and specificity (85%) for diagnosing AUC.<sup>17</sup>

Although some authorities have recommended that urine culture and antimicrobial-susceptibility testing be performed for any patient with a suspected UTI, routine pretherapy urine culture is not always recommended in AUC. Patients with consistent symptoms and characteristic urinalysis findings are often treated with empiric therapy because the bacteriology is predictable. In usual clinical practice, therapy for AUC is often completed before culture results would be known.<sup>2,26</sup>

Rapid urine tests to support a diagnosis of AUC include direct microscopic examination of fresh or gram-stained urine and dipstick tests such as the leukocyte esterase (LE) test and the LE/nitrite strip. Pyuria is present in nearly all women with acute, symptomatic UTIs. Pyuria without significant bacteriuria suggests urethritis. The LE test has a reported sensitivity of 75% to 96% and specificity of 94% to 98% in detecting >10 leukocytes per high-power field, or ≥10<sup>5</sup> uropathogen CFU/mL of urine.<sup>17</sup>

**Optimizing Diagnostic Measures**

The utility of measures for diagnosing AUC in healthy women was reviewed recently. Nine studies that provided original data on the accuracy of history or physical examination, including sufficient data to allow for calculation of likelihood ratios (LRs) for acute UTIs, were included.<sup>27</sup> Table 5 summarizes the LRs for 10 signs and symptoms of UTI. A higher positive LR indicates that presence of the symptom

**Table 5****Clinical Predictors of UTI**

Symptom	Positive LR (95% CI)	Negative LR (95% CI)
Self-diagnosis	4.0 (2.9-5.5)	0.0 (0.0-0.1)
Hematuria	2.0 (1.3-2.9)	0.9 (0.9-1.0)
Frequency	1.8 (1.1-3.0)	0.6 (0.4-1.0)
Fever	1.6 (1.0-2.6)	0.9 (0.9-1.0)
Flank pain	1.1 (0.9-1.4)	0.9 (0.8-1.1)
Back pain	1.6 (1.2-2.1)	0.8 (0.7-0.9)
Dysuria	1.5 (1.2-2.0)	0.5 (0.3-0.7)
Lower abdominal pain	1.1 (0.9-1.4)	0.9 (0.8-1.1)
Vaginal discharge	0.3 (0.1-0.9)	3.1 (1.0-9.3)
Vaginal irritation	0.2 (0.1-0.9)	2.7 (0.9-8.5)

LR = likelihood ratio; CI = confidence interval.

Adapted with permission from Bent S, et al. *JAMA*. 2002;287:2705-2706. Copyright 2002, American Medical Association.

increases the likelihood of a UTI diagnosis, and a higher negative LR indicates that presence of the symptom decreases the likelihood of a UTI diagnosis.

The signs and symptoms most predictive of a correct UTI diagnosis are hematuria, frequency, back pain or costovertebral tenderness, and dysuria. Each of these by itself increases the likelihood of UTI to approximately 50%. The symptoms that most decrease the likelihood of a diagnosis of uncomplicated UTI are vaginal discharge and vaginal irritation. Combinations of these signs and symptoms, whether positive or negative, are more powerful predictors. For example, the presence of dysuria and frequency along with the absence of vaginal discharge and vaginal irritation increases the LR of UTI. Absence of dysuria when vaginal discharge and irritation are present decreases the LR of UTI.<sup>27</sup> Symptoms that suggest pyelonephritis rather than uncomplicated cystitis include fever, symptoms that persist beyond 7 days, and costovertebral tenderness or flank pain.<sup>28</sup>

Women who have had previous UTIs are knowledgeable about their own symptoms and are able to self-diagnose accurately. A study of self-diagnosis with patient-initiated management demonstrated that this approach was appropriate for the treatment of RUTIs. As an alternative to prophylaxis with antimicrobials, self-treatment may decrease antimicrobial use while alleviating symptoms promptly. In a university-based study, 88 of 172 women self-diagnosed 172 UTIs, verified in clean-catch urine specimens prior to initiation of treatment. In 144 cases (84%), culture was

positive. Based on these data, the positive LR for self-diagnosis is 4.0, and the negative LR is 0.0.<sup>27,29</sup>

Dipstick urinalysis is a useful test to support a diagnosis of AUC; it may be the only evaluation needed. The probability of a UTI diagnosis for a woman with symptoms and a positive dipstick test is 81%. The combination of LR and nitrite tests increases specificity at the expense of sensitivity. With a sensitivity of 75% and specificity of 82%, the positive LR for dipstick analysis is 4.2, and the negative LR is 0.3.<sup>27</sup>

With a combination of signs/symptoms and rapid urine tests, clinicians usually can diagnose AUC with sufficient confidence to initiate treatment promptly. When history suggests a urinary syndrome other than AUC, further diagnostic evaluation, including urine culture, may be necessary.

### The Challenge of Antimicrobial Resistance in Treating AUC

Resistance of bacteria to antimicrobials has been identified as a major concern by national medical organizations, including the Infectious Diseases Society of America (IDSA) and the Food and Drug Administration (FDA).<sup>30,31</sup> Previously a problem primarily in hospitals, antimicrobial resistance is now an important concern in the context of community-acquired infection.

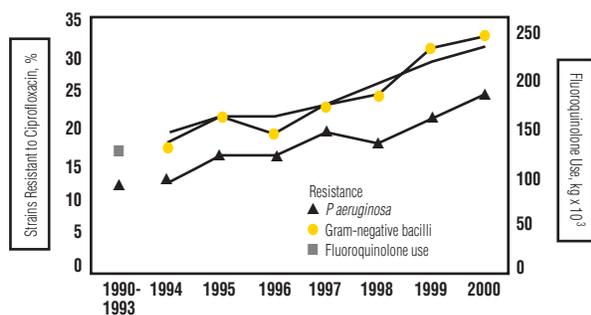
The mechanisms of resistance are well understood. Every organism has the capacity to respond to environmental threats with genetic alterations. Within a population of bacteria exposed to an antimicrobial, strains with resistance will survive and reproduce. Thus, antimicrobial pressure leads to evolution of a bacterial population of increased resistance.

It has also been shown that decreased susceptibility is directly correlated with increased antibiotic use. The overall susceptibility of gram-negative bacilli to ciprofloxacin has declined from 86% in 1994 to 76% in 2000. This directly correlates with a 2.5-fold increase in the use of quinolones over the past 10 years (Figure 2).<sup>32</sup>

Inappropriate prescribing of antimicrobials is thought to be a major contributor to increased antimicrobial resistance. From 20% to 50% of antibiotic prescriptions in community settings and 25% to 45% in hospital settings are inappropriate in selection of agent, dose, or treatment duration. Of an estimated 345 million annual prescriptions, between 75 million and 150 million may be inappropriate. Of particular concern is the prescription of antibiotics for viral infections, for which they are ineffective. Contributing to excess use is pressure from patients or management guidelines, which substitute drug therapy for diagnostic tests.

Figure 2

### Fluoroquinolone Use and Resistance Rates in *Pseudomonas aeruginosa* and Gram-Negative Bacilli



National fluoroquinolone-use data were obtained from IMS HEALTH Retail and Provider Perspective (Plymouth Meeting, Pa). The increasing rates of ciprofloxacin resistance correlate with the steadily increasing fluoroquinolone use ( $r=-0.976$ ,  $P<.001$  for *P. aeruginosa*;  $r=0.891$ ,  $P=.007$  for gram-negative bacilli;  $r=0.958$ ,  $P<.001$  for years of observation). The 1990-1993 data points represent composite susceptibility and fluoroquinolone use for those 4 years.

Reprinted from Neuhauser MM, Weinstein RA, Rydman R, Danziger LH, Karam G, Quinn JP. *JAMA*. 2003;289:885-888.

An additional problem is prescription of broad-spectrum agents when a targeted-spectrum agent would be equally effective and may have less selective pressure for resistance.<sup>30</sup> In fact, antibacterial resistance has become such a problem that the FDA has amended its regulations to require labeling for all systemic antibacterial drug products to include certain statements about using antibiotics in a way that will reduce the development of drug-resistant bacterial strains, effective as of February 6, 2004.<sup>31</sup> In addition to encouraging clinicians to use antibiotics only where bacterial infections are strongly suspected (vs viral infections) and patient counseling regarding appropriate use, the FDA also recommends that the clinicians refer to their local epidemiology and susceptibility patterns in the absence of culture and susceptibility data.

Currently, antimicrobial resistance is a problem in the management of many infections. A multinational surveillance program reported that 92% of community-acquired respiratory isolates of *Moraxella catarrhalis* produce  $\beta$ -lactamase, so previous first-line agents used for respiratory bacterial infections, such as amoxicillin, are no longer effective for this pathogen. Some strains of *Enterococcus faecalis*, *Mycobacterium tuberculosis*, and *P aeruginosa* are resistant to almost all antibiotics available. The impact of resistance on therapeutics is now considered urgent, because resistance to even relatively new agents emerges quickly and novel antimicrobials are not being developed to keep pace with the threat.<sup>30</sup>

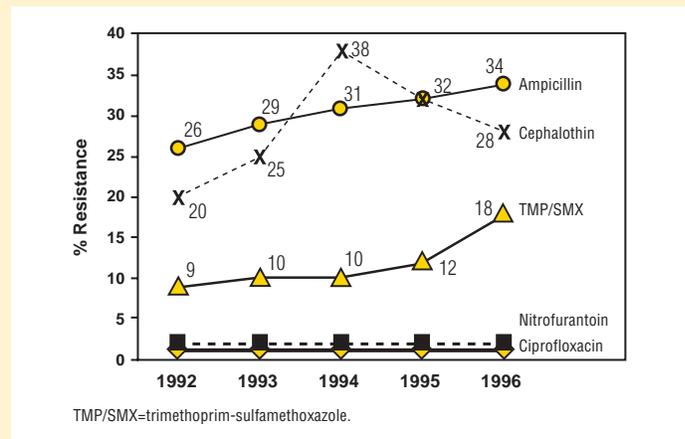
### Emerging Resistance in Uropathogens

The current IDSA treatment guidelines for AUC recommend a 3-day regimen of TMP/SMX. This agent has been in use for AUC for more than 20 years and has been highly effective. The IDSA guidelines, however, also suggest that in areas where the prevalence of resistant pathogens is 10% to 20% or higher, alternatives should be considered for empiric therapy. In most parts of the United States, the 10% resistance threshold of *E coli* to TMP/SMX has been crossed, and, in some areas, the prevalence of resistance is 20%. For other agents, such as amoxicillin, the prevalence is 20% to 30%, and this agent is no longer recommended as empiric therapy for UTI.<sup>28,33,34</sup>

Figure 3 shows changes in resistance of *E coli* isolates causing AUC in women over a 4-year span. The data include urinary isolates from more than 4000 ambulatory HMO patients who were treated for acute cystitis. More than 95% of the cases were confirmed as AUC by chart review. The most frequent pathogens were *E coli* (86%), *S saprophyticus* (4%), *Proteus* spp (3%), and *Klebsiella* spp (3%).<sup>35</sup>

Figure 3

### Prevalence of Resistance Among *Escherichia coli* Isolates Causing AUC in Women



Adapted from Gupta K, Scholes D, Stamm WE. *JAMA*. 1999;281:736-738.

The prevalence of resistance to the 2  $\beta$ -lactam agents ampicillin and cephalothin was 20% or higher in 1992 and increased to more than 30% within 2 years. There was a similar prevalence of resistance for *E coli* and other urinary pathogens. Thus, these agents are no longer effective for empiric treatment of AUC.<sup>35</sup>

The increase in resistance to TMP/SMX is relevant to current treatment of AUC. In 1992, resistance to TMP/SMX in urinary *E coli* was 9%. This doubled in 4 years. The increase in resistance was similar in the non-*E coli* isolates, starting at 8% and doubling in 4 years.<sup>35</sup> These data suggest that alternative agents for empiric management of AUC may need to be considered.

### Regional Variation in Resistance

Resistance rates are not uniform across the United States. It is important for clinicians to use knowledge of local resistance prevalence data in selecting antibiotics.<sup>36</sup> The IDSA guidelines also urge continuing surveillance to monitor changes in the susceptibility of uropathogens.<sup>37</sup>

To identify trends in resistance of common uropathogens (*E coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *S saprophyticus*) to 4 drugs commonly used to treat UTIs, nearly 6000 urinary isolates from laboratories in 43 states were reviewed. The agent with the lowest rates of resistance in the 2 pathogens most commonly causing AUC (*E coli* and *S saprophyticus*) was nitrofurantoin (Table 6, page 8).<sup>38</sup> The highest resistance in *E coli* to TMP/SMX was in Iowa, at 33%, and the lowest in Pennsylvania, at 7.4%. The rate in Arizona was 43.7%, but data from only 33 *E coli* isolates were available. Region-to-region

variation was also considerable, ranging from a high of 28.4% in the West-South-Central region to a low of 9.2% in the neighboring East-South-Central region.<sup>38</sup> Figure 4 shows the regional susceptibility of *E coli* to TMP/SMX, ciprofloxacin, and nitrofurantoin in all urinary infections, including but not exclusively AUC.<sup>39</sup> Such surveillance data may overestimate the prevalence of drug resistance, especially since urine cultures are seldom obtained pretreatment. Often, only patients suspected of having resistant uropathogens are cultured, introducing a bias toward more resistant organisms. However, these data are important in showing potential resistance trends in various regions of the United States.

**Table 6**

**Nationwide Resistance Rates of Common Uropathogens to Frequently Used Antibiotics**

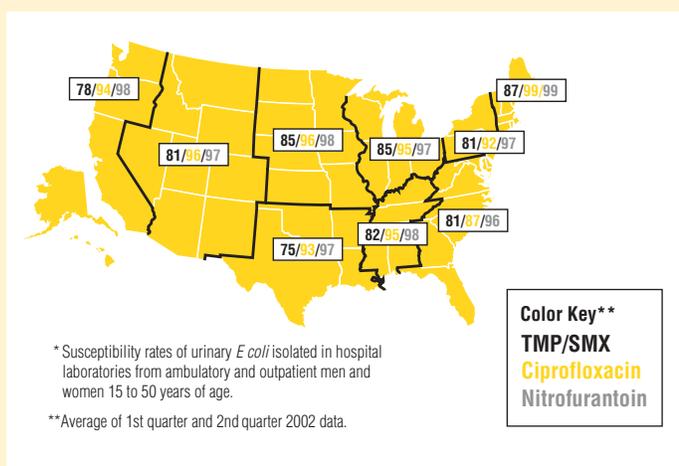
	Percent of Resistant Isolates <i>E coli</i>	<i>S saprophyticus</i>
Nitrofurantoin	0.5	0.0
Ciprofloxacin	1.8	0.4
Cephalothin	9.7	1.0
TMP/SMX	16.8	3.0

TMP/SMX=trimethoprim-sulfamethoxazole.

Adapted from *Int J Antimicrob Agents*, Vol. 18, Karlowsky JA, et al. Prevalence of antimicrobial resistance among urinary tract pathogens isolated from female outpatients across the US in 1999, 124, Copyright 2001, with permission from Elsevier.

**Figure 4**

**Geographic Variation in Percent of Antimicrobial *E coli* Susceptibility of TMP/SMX, Ciprofloxacin, and Nitrofurantoin\***



Source: TSN® Database-USA, Copyright 2002, Focus Technologies, Inc. Available at: <http://www.med-scape.com/pages/editorials/resourcecenters/public/uti/regions>. Accessed April 14, 2003.

**Resistance Trends in Other Countries**

Resistance of uropathogens to drugs used to treat AUC is a problem in countries outside the United States. Particularly high rates of resistance to TMP/SMX have been reported in Israel (31%), Spain (32%), and Bangladesh (60%).<sup>28</sup> Although the prevalence of resistance to ciprofloxacin and other fluoroquinolones has generally remained low, it has reached 18% in Bangladesh and 4% in Israel. Resistance to norfloxacin is 13% in Spain.<sup>28</sup>

Studies have described the reasons for the increase in resistance. In a Dutch review including 90,000 *E coli* isolates, resistance in these isolates to norfloxacin increased from 1.3% to 5.8% between 1989 and 1998. This increase coincided with a doubling in norfloxacin prescriptions from 1990 to 1997. During this same period, *E coli* resistance to nitrofurantoin remained stable, ranging from just above 6% to just below 5%. Resistance rates to TMP and amoxicillin were, respectively, approximately 25% and 35%.<sup>40</sup>

A Spanish study reported an increase from 3% to 20% ( $P < .00001$ ) in ciprofloxacin resistance in *E coli* isolates from urine culture at the investigators' 250-bed institution. This was recorded at the same time as an increase in fluoroquinolone use from 1392 to 3203 g annually ( $P < .05$ ). The investigators observed that the fluoroquinolones usually were used as empiric therapy for infections for which these drugs are not considered first-line agents, including uncomplicated UTI.<sup>41</sup>

**Multiple-Drug Resistance**

Multiple-drug resistance (MDR) refers to bacterial strains with resistance to several different antimicrobial classes. The occurrence of MDR may greatly increase the difficulty of treating an infection. Although it is not unexpected, for instance, that pathogens producing  $\beta$ -lactamase are generally resistant to many  $\beta$ -lactam agents and that resistance to one fluoroquinolone usually results in resistance to all fluoroquinolones, resistance to antimicrobials of multiple classes adds further complexity to treatment. MDR was described in a collection of 123,691 *E coli* isolates, 38,835 of which were tested against ampicillin, cephalothin, ciprofloxacin, nitrofurantoin, and TMP/SMX. Of these isolates, 7.1% (2763) were considered multiple drug resistant, defined as being resistant to 3 or more agents. Overall, resistance rates of isolates tested against single drugs are shown in Table 7.<sup>42</sup>

Studies have indicated that multiple-drug resistant strains are likely to be resistant to  $\beta$ -lactams (penicillins and cephalosporins) as well as to TMP/SMX.<sup>42,43</sup> Pathogens resistant to one  $\beta$ -lactam frequently exhibit cross-resistance to others. Resistance to quinolones as a class has been

slow to appear, but some *E coli* express mutated target genes. Strains resistant to ciprofloxacin usually exhibit resistance to other quinolones. A recent, large, nationwide study found that ciprofloxacin-resistant bacteria exhibited resistance not only to fluoroquinolones but also to broad-spectrum antimicrobials of other classes, leading authors to conclude that more judicious use of fluoroquinolones is necessary.<sup>32</sup>

### Clinical Effects of Resistance

Although it seems evident that treating an infection with an antimicrobial agent to which the pathogen is resistant will lead to treatment failure and recurrence, the situation is not clear-cut for UTI. The correlation between clinical outcome and in vitro susceptibility data is not precise. In vitro susceptibility data use a minimum inhibitory concentration (MIC) of the drug needed to eradicate 90% of the reference pathogen. A pathogen is considered susceptible when the serum or urine drug level exceeds the MIC. The antimicrobials most frequently used to treat UTIs achieve urinary concentrations much higher than their serum levels because they are excreted into the urine. Thus, MIC values developed for serum levels may not be relevant to UTI outcomes. Since clinical trials often exclude patients with uropathogens resistant to the drugs being studied, information is not widely available about outcomes when UTI is treated with an agent to which the organism is resistant.<sup>28</sup>

One observational study evaluated the effectiveness of TMP/SMX in treating uncomplicated UTIs due to TMP/SMX-resistant pathogens.<sup>44</sup> For 71% of 544 patients, cultures grew TMP/SMX-susceptible bacteria, and, for 29%, TMP/SMX-resistant organisms were isolated. *E coli* was the most common infecting organism in both groups. The rates of bacteriologic cure were significantly different between the 2 groups: 86% of 333 women infected with TMP/SMX-susceptible bacteria had sterile post-treatment cultures compared with 42% of 151 women with TMP/SMX-resistant strains ( $P < .001$ ). Clinical cure rates were also significantly different: 88% of 333 women infected with TMP/SMX-susceptible strains and 54% of 151 women infected with TMP/SMX-resistant strains. The authors concluded that in high-resistance areas, TMP/SMX is not an appropriate empiric drug.<sup>44</sup>

In a recent retrospective study in the United States, the prevalence of TMP/SMX resistance to *E coli* increased from 8.1% to 15.8% between 1992 and 1999 ( $P = .01$ ). Women who had recently (within 2 weeks) received TMP/SMX were 16 times more likely to be infected with a TMP/SMX-resistant organism than were those who had not taken any antibiotics within the previous 2 weeks. Women

**Table 7**

### Antimicrobial Susceptibility of 123,691 *E coli* Urinary Tract Isolates

Drug	Total No. of Isolates Tested	% Susceptible	% Intermediate	% Resistant
Ampicillin	122,519	60.1	0.8	39.1
TMP/SMX	123,691	81.4	—	18.6
Cephalothin	49,667	70.4	14.0	15.6
Ciprofloxacin	107,342	96.2	0.1	3.7
Nitrofurantoin	105,595	98.1	0.9	1.0

Adapted with permission from Sahn DF, et al. *Antimicrob Agents Chemother.* 2001;45:1403:1402-

infected with a TMP/SMX-resistant organism and treated with TMP/SMX were 17 times more likely to have treatment failure.<sup>45</sup>

Some smaller studies have also concluded that outcomes are poor when the *E coli* isolate is resistant to TMP/SMX. In a study in the United Kingdom, 14 of 135 women with AUC assigned to receive TMP/SMX had resistant infections. Bacterial eradication was achieved by 7 of these women (50%) at day 14 compared with 106 (86%) of 123 women whose infecting pathogens were not resistant to TMP/SMX. In another small study, 5 of 10 women with uropathogens resistant to TMP/SMX achieved bacterial eradication, and 6 attained clinical cure. Thus, clinical failure rates far exceed the anticipated failure rate for uropathogens susceptible to TMP/SMX.<sup>28</sup>

Since empiric treatment without pretreatment urine culture or susceptibility testing is likely to remain the strategy of choice for AUC, it would be helpful to be able to predict which patients are likely to have infection with resistant pathogens. A case-control study with 448 patients identified 4 factors predictive of TMP/SMX resistance in a multivariate analysis. These were diabetes, recent hospitalization, current use of any antibiotic, and recent use of TMP/SMX. Of these, the strongest predictor of resistance was recent use of TMP/SMX (odds ratio, 5.1; 95% confidence interval [CI], 2.2-11.5).<sup>46</sup>

Another important question is to what extent the empiric use of broad-spectrum antibiotics such as TMP/SMX and the fluoroquinolones contributes to the general growth of resistance, potentially impairing the utility of these drugs in treating more serious diseases. Recently, the FDA noted that using broad-spectrum antibiotics, including newer drugs, “can increase the development of resistance.”<sup>31</sup> TMP/SMX has indications not only for UTI but also for acute otitis media, acute exacerbation

of chronic bronchitis, shigellosis, *Pneumocystis carinii* pneumonia, and "traveler's diarrhea."<sup>47</sup> Ciprofloxacin has indications for UTI, lower respiratory infections, some nosocomial pneumonias, skin and skin structure infections, bone and joint infections, complicated intra-abdominal infections, acute sinusitis, and chronic bacterial prostatitis.<sup>48</sup> Both of these drugs are used off-label frequently

as treatment or prophylaxis for a wide range of presumed bacterial infections. A notorious example is the huge ciprofloxacin use in September 2001 following the anthrax episodes in the United States. Even before that event, however, *E coli* resistance to ciprofloxacin had been increasing in a stepwise fashion each year,<sup>36</sup> and, in some areas of the United States, uropathogenic *E coli* resistance to ciprofloxacin has reached or passed the 10% level.<sup>36</sup>

In contrast to the broad-spectrum agents, nitrofurantoin and fosfomycin are narrowly targeted antimicrobials used to treat AUC only. Nearly all uropathogenic strains of *E coli* are susceptible to both drugs. The activity of nitrofurantoin against the second most frequent urinary pathogen, *S saprophyticus*, approaches 100%; fosfomycin does not have an indication for treating infections caused by this pathogen. Nitrofurantoin has been in use for nearly 50 years with negligible resistance in the usual uropathogens. It is not used as a growth promoter in animal husbandry, and, since it is not structurally related to other antimicrobials, even in rare cases where resistance does emerge, cross-resistance to other drugs used in serious infections is not likely.<sup>28,49</sup> Thus, these drugs do not currently encounter high levels of resistance and would not promote clinically important resistance that might interfere with effective treatment of other infections.

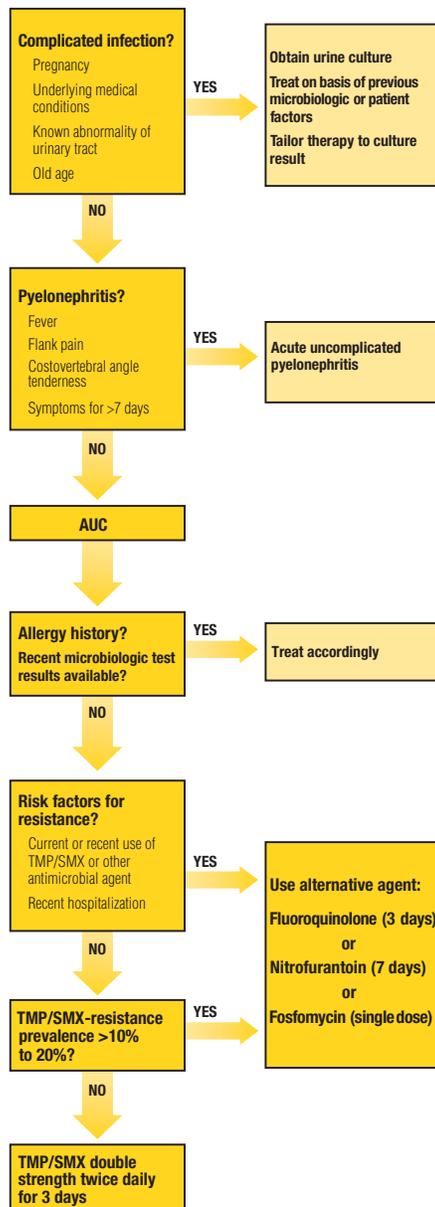
### Optimal Treatment for AUC

The ideal treatment strategy for AUC would be an antimicrobial regimen that could be initiated as soon as symptoms were identified, was specifically targeted to the infecting pathogen, provided prompt resolution of symptoms, minimized recurrence, and did not promote resistance. Some of these characteristics appear to be in conflict, ie, immediate therapy and therapy targeted to the causative organism. To identify the specific organism, urine culture and susceptibility testing must be available, precluding empiric therapy. Because *E coli* and *S saprophyticus* cause approximately 90% of AUC and prompt symptom resolution is, from the patient's perspective, desirable, empiric antimicrobial therapy effective against those 2 pathogens seems most appropriate.

Figure 5 is an algorithm to assist clinicians in selecting appropriate treatment. An initial step is confirming the diagnosis of AUC: The site of infection is the bladder and not the kidney, and the infection is uncomplicated. Healthy, ambulatory women with symptoms only of AUC are assumed to have uncomplicated infections, and these patients may be treated empirically. A patient with an equivocal diagnosis should have a urine

Figure 5

### Strategy for Management of Uncomplicated Community-Acquired UTI in Women



Adapted with permission from Gupta K, Hooton TM, Stamm WE. *Ann Intern Med.* 2001;135:41-50.

culture, and antibiotics should be tailored to the results. A patient for whom empiric therapy fails should also have a urine culture and susceptibility testing to guide further treatment.<sup>28</sup>

When symptoms are consistent with pyelonephritis, urine culture and susceptibility testing are recommended before therapy is initiated. Acute uncomplicated pyelonephritis is a more serious disease than AUC and requires a longer course of therapy. Fluoroquinolones are considered the optimal agents for oral treatment of acute uncomplicated pyelonephritis. In some cases, an initial intravenous dose of an antimicrobial such as ciprofloxacin or ceftriaxone is given. Fosfomycin and nitrofurantoin are not indicated for oral treatment of acute uncomplicated pyelonephritis. Resistance trends in pathogens causing pyelonephritis are similar to those for acute cystitis, and the increasing prevalence of TMP/SMX resistance is of particular concern. Resistance should be considered when therapy is selected.<sup>28</sup>

### Considerations in Antibiotic Selection

No single antibiotic is the ideal choice for all cases of AUC. The clinician must consider several issues in selecting the most appropriate option.

#### **Broad- versus narrow-spectrum antimicrobials.**

Broad-spectrum antibiotics treat infections caused by a wide range of bacteria, including the most common uropathogens in AUC. Several broad-spectrum antimicrobials have lost some efficacy for AUC and other infections because of increasing resistance. Narrow-spectrum antibiotics are for AUC only, and their efficacy against the most common uropathogens remains high. They are less affected by pathogenic resistance and less likely to induce resistance in pathogens that cause other important infections.

**Length of treatment.** The recommended length of treatment ranges from 1 to 7 days, depending on the antimicrobial agent and selected patient characteristics. Shorter treatment regimens are associated with higher rates of adherence and fewer adverse drug effects. One-day treatment courses have been associated with lower cure rates and higher recurrence rates for TMP/SMX, amoxicillin, and the fluoroquinolones and have not been studied for nitrofurantoin.<sup>37</sup> They may be less effective for women with a long duration of symptoms (more than 7 days) before treatment or for postmenopausal women.

### Antibiotic Options

**TMP/SMX.** A double-strength tablet of TMP/SMX contains 160 mg of TMP and 800 mg of SMX. This is currently the first-line empiric therapy for AUC, although increasing resistance in uropathogens may be limiting its effectiveness. TMP/SMX is

active against most uropathogens, including *E coli*, *Klebsiella* spp, *Enterobacter* spp, and *P mirabilis*, but not against *Pseudomonas* spp and *Enterococcus* spp. TMP/SMX double-strength tablets can be given BID for 3 days to women with AUC. TMP also may be used by itself. Fewer adverse effects are encountered with TMP alone than with TMP/SMX.<sup>50</sup> The most common adverse effects are allergic skin reactions, primarily due to the sulfa component, and gastrointestinal disturbance. TMP and TMP/SMX are contraindicated in the first trimester of pregnancy because of inhibition of folate metabolism.<sup>51</sup> TMP/SMX is also contraindicated for nursing mothers and is not recommended for use in children less than 2 months of age.<sup>52</sup>

**Fluoroquinolones.** The fluoroquinolone currently most widely used in the United States is ciprofloxacin, although there are many other fluoroquinolones available. These antimicrobials are active against nearly all gram-negative aerobes and most community-acquired gram-positive pathogens (with the exception of *Enterococcus* spp). The fluoroquinolones attain very high urinary concentrations, more than 100 times peak plasma levels, making these drugs very effective in treating both uncomplicated and complicated UTIs. The targets are DNA gyrase or DNA topoisomerase. Mutation in these enzymes leads to resistance. Alteration in the DNA gyrase or topoisomerase usually confers cross-resistance to other fluoroquinolones. Increasing use of fluoroquinolones for a wide variety of indications may result in increasing resistance. Any dose of ciprofloxacin leads to low levels in nasal secretions and saliva, promoting resistance in respiratory pathogens such as *S pneumoniae*.<sup>53</sup> Fluoroquinolones are contraindicated for patients less than 18 years of age because of the risk of potential arthropathy.<sup>50</sup> Their use in pregnancy is not recommended because of potential arthropathy of the fetus.<sup>51</sup> Uncommon side effects include liver toxicity and QT interval prolongation.<sup>15,50</sup>

**Nitrofurantoin.** Nitrofurantoin has been in use to treat AUC for almost 50 years. The initial microcrystalline formulation had a high incidence of gastrointestinal side effects, which are avoided with the current macrocrystalline and slow-release preparations. Nitrofurantoin is metabolized by bacterial nitroreductases, forming reactive metabolites that inhibit bacterial ribosomal proteins at several synthetic levels, completely disrupting bacterial protein synthesis.<sup>50</sup> The multiple bacterial targets of this drug may be the reason resistance has not developed in uropathogens despite prolonged use.<sup>54</sup> Nitrofurantoin is highly active against the most common uropathogens, *E coli* and *S saprophyticus*, and has some activity against several other uropathogens including *Klebsiella* spp. It is not

effective for *P mirabilis* or *P aeruginosa*. Nitrofurantoin is a urospecific drug that reaches high urine concentrations but does not have systemic antimicrobial activity. This urinary tract specificity results in minimal effects on host vaginal and fecal flora. Nitrofurantoin should be given for 7 days, either 100 mg BID (slow release) or 50 mg QID (macrocrystalline). Nitrofurantoin does not achieve therapeutic levels in the renal parenchyma and cannot be used for treatment of renal infection.<sup>50</sup> The adverse event of greatest concern with nitrofurantoin is acute interstitial pneumonitis, which occurs rarely and resolves with rapid withdrawal of the drug.<sup>50</sup> Nitrofurantoin is safe for use in children more than 1 year of age and in pregnancy (Category B), but it should be avoided during labor and delivery.<sup>51,55</sup>

**Fosfomycin.** Fosfomycin tromethamine was approved in the United States for treatment of AUC in 1996. It is highly active against gram-negative rods, including most Enterobacteriaceae. Gram-positive bacteria are less sensitive to fosfomycin than are gram-negative bacteria. Fosfomycin is effective against *E coli* and *E faecalis* but is not approved for treating infections caused by *S saprophyticus*.<sup>28</sup> Its mechanism of action is due to the inactivation of the enzyme enolpyruvyl transferase. The bioavailability of fosfomycin is high, and a single 3-g dose reaches therapeutic concentrations in the urine for 1 to 3 days.<sup>54</sup> Fosfomycin is relatively free of side effects, although diarrhea may be common.<sup>54</sup> It is a Category B drug for pregnancy, so the risk of untreated disease may outweigh the risks of treatment. The safety of fosfomycin for patients less than 12 years of age has not been established.<sup>56</sup>

### *Clinical and Bacteriologic Response*

Clinical and bacteriologic response rates are of principal importance in the choice of an antimicrobial for AUC (Table 8).<sup>48,56-66</sup> A 3-day ciprofloxacin course was compared with 7 days of TMP/SMX and nitrofurantoin. Evaluation was at 4 to 10 days after the end of treatment and 4 to 6 weeks later. At the end of therapy, bacteriologic eradication was reported in 88% of ciprofloxacin patients, 93% of TMP/SMX patients, and 86% of nitrofurantoin patients. Four to 6 weeks later, the bacterial eradication rate was highest in the ciprofloxacin group (91%), followed by nitrofurantoin (82%) and TMP/SMX (79%). Clinical resolution was similar for the 3 groups; at the 4- to 6-week follow-up, 90% of ciprofloxacin and TMP/SMX patients and 89% of nitrofurantoin patients were clinically cured.<sup>67</sup>

Other factors to consider in selecting an antimicrobial include safety, risk of resistance, and such patient characteristics as age, pregnancy status, and history of allergy or sensitivity to the drug.

Fortunately, some antimicrobials are available with a long experience that documents safety and efficacy in treating uncomplicated UTIs.

### **Prevention of RUTI**

Since 20% to 30% of women experience RUTIs within 3 to 4 months of initial infection, prevention is an important therapeutic goal.<sup>4</sup> Approaches to prevention that have been considered have been both pharmacologic and nonpharmacologic.

There are a variety of strategies to manage RUTI, including continuous low-dose prophylaxis and post-coital prophylaxis.<sup>68</sup> Antimicrobials systematically studied for prophylaxis include TMP alone, TMP/SMX, norfloxacin, and nitrofurantoin. They have been shown to be highly effective in preventing UTI recurrence,<sup>68-70</sup> although other antimicrobials that are effective in the treatment of UTI have also been used in clinical practice. A concern with prophylactic use of antimicrobials is the risk of creating resistance in host flora. Although resistance has not been significant in most studies,<sup>68</sup> it can be problematic, and antimicrobials with current low resistance rates are preferred. The best determinant of the likely success of an antimicrobial agent is the susceptibility patterns of that agent against the most common uropathogens in the community.<sup>68</sup>

Given the frequency of RUTIs, nonpharmacologic preventive approaches are appealing. The most popular of these is the use of cranberry juice. Cranberries, blueberries, and other berries of the *Vaccinium* species contain condensed tannins called proanthocyanidins, which can prevent adhesion of *E coli* to the cell surface of the endothelium. Another popular nonpharmacologic approach uses lactobacilli to restore the normal vaginal flora and prevent colonization with uropathogens. A prospective, randomized study enrolled 150 women and compared cranberry-lingonberry juice with a *Lactobacillus* drink or placebo. Women receiving the fruit juice had 20% fewer RUTIs than did the placebo and *Lactobacillus* groups.<sup>71</sup>

*Lactobacillus* is part of a treatment category called *probiotics*, exogenous microorganisms administered to promote the health of the host by treating or preventing disease. Advocates of this approach to treating RUTIs claim that selected strains of lactobacilli can colonize the vagina and inhibit colonization by potential uropathogens. These strains are currently being tested to measure their efficacy in prevention of bacterial vaginosis.<sup>72</sup>

The validity of certain nonpharmacologic approaches to prevention remains questionable. As long as these approaches do no harm and have the possibility of doing some good, they may be worth a trial. The decision will be based on

patient factors, such as frequency and impact of RUTIs on the patient's quality of life.

Frequent RUTIs affect 10% to 15% of women over 60 years of age. Postmenopausal women experience changes in vaginal mucosa that favor colonization by pathogens, including an increase in vaginal pH, a reduction of colonization by lactobacilli, and colonization by Enterobacteriaceae. A controlled study evaluated the nightly use of an intravaginal estriol cream for 2 weeks followed by twice-weekly applications for 8 months, compared with a placebo cream used in the same manner. After 4 months of treatment, the cumulative likelihood of remaining disease free was 0.95 (95% CI, 0.88-1.0) in the estrogen group versus 0.30 (95% CI, 0.16-0.46) in the placebo group. Women in the estrogen group had a significantly lower rate of RUTIs than did

controls ( $P < .001$ ). In women who used the estriol cream, vaginal pH decreased, colonization with Enterobacteriaceae decreased, and colonization with lactobacilli increased.<sup>73</sup>

The goal of prophylaxis is to minimize the impact of RUTIs on patients. The strategy of self-diagnosis and patient-initiated treatment is not prophylaxis, but it may accomplish the same objective. Women who experience recurrent AUC can reliably identify infection in themselves. With self-initiation of treatment under the guidance of a clinician, the time between symptom onset and resolution can be reduced.<sup>29</sup>

### Treating UTI in Special Populations

UTIs in certain patient populations may require special consideration. The infecting bacteria may

**Table 8**

### Commonly Used Antimicrobial Agents for Acute Uncomplicated Cystitis

Drug	Regimen	Clinical Response/ Resolution*	Bacteriologic Response*	Mechanism of Action (MOA)†	Resistance Trends Among <i>E coli</i>
TMP/SMX	160 mg TMP/800 mg SMX BID X 3 d	90% <sup>57</sup>	94%-96% <sup>57</sup>	TMP blocks tetrahydrofolic acid production; SMX inhibits bacterial synthesis of dihydrofolic acid	↑↑
Nitrofurantoin monohydrate/ macrocrystals	100 mg BID X 7 d	89%-94% <sup>58</sup>	78%-79% <sup>58</sup>	Inhibits protein synthesis, aerobic energy metabolism, DNA/RNA synthesis, and cell wall synthesis	—
Nitrofurantoin macrocrystals	50 mg QID X 7 d	90%-92% <sup>58</sup>	72%-76% <sup>58</sup>	Inhibits protein synthesis, aerobic energy metabolism, DNA/RNA synthesis, and cell wall synthesis	—
Fosfomycin tromethamine	3-g sachet (SDT)	80% <sup>56,60</sup>	70%-78% <sup>59,60</sup>	Inactivates enzyme enolpyruvyl transferase; interferes with DNA gyrase	↑
Ciprofloxacin	100 mg BID X 3 d	87%-95% <sup>48,61</sup>	91%-97% <sup>48,61</sup>	Interferes with DNA gyrase	↑
	250 mg BID X 3 d	93%-94% <sup>61,62</sup>	90% <sup>61,62</sup>		
	250 mg BID X 7 d	92%-94% <sup>48,62</sup>	97% <sup>48,62</sup>		
	500 mg QD X 3 d	95% <sup>59,63</sup>	94% <sup>59,63</sup>		
Levofloxacin	250 mg QD X 3 d	98% <sup>64</sup>	96% <sup>64</sup>	Inhibits topoisomerase IV and DNA gyrase	?‡
Gatifloxacin	200 mg QD X 3 d	95% <sup>65</sup>	93% <sup>65</sup>	Inhibits topoisomerase IV and DNA gyrase	?
	400 mg SDT	90% <sup>66</sup>	95% <sup>66</sup>		

SDT = single-dose therapy.

\*Responses measured varied per study from 1 to 14 days posttherapy.

†MOA based on drug package inserts.

‡Trends not established.

vary, and not all antimicrobials are suitable for pediatric use or for pregnant women. Other patient characteristics may necessitate changes in antimicrobial selection or regimen. In children and elderly patients, infections are frequently complicated and will require different approaches to investigation and treatment than do uncomplicated infections.

### *Infants and Children*

UTIs in children may have greater morbidity or long-term consequences, including impaired renal function, hypertension, end-stage renal disease, and complications of pregnancy in adulthood. RUTI may progress to pyelonephritis, with the risk of renal scarring. When UTI is diagnosed in children, genitourinary abnormalities should be excluded.<sup>15</sup>

Fluoroquinolones such as ciprofloxacin are contraindicated for patients less than 18 years of age, and fosfomycin has not been studied in children less than 12 years of age. Nitrofurantoin and TMP/SMX are both considered safe for use in children more than 1 year of age.<sup>47,55</sup> A meta-analysis of 16 randomized, controlled trials comparing long- and short-course therapy in children has concluded that to minimize risks of pyelonephritis and renal scarring, a 7- to 14-day treatment course is preferable to a 3-day course of therapy.<sup>74</sup>

### *Pregnant Women*

During pregnancy, bacterial growth is favored by increasing content of amino acids, vitamins, and other nutrients in urine. Dilatation of the urinary tract, due to hormonal and mechanical factors, may also lead to stasis and promote infection.<sup>51</sup> Pyelonephritis is one of the most frequent causes of hospitalization during pregnancy. Because ASB leads to pyelonephritis, it must be identified and treated in pregnant women. In a Spanish center, a program to screen and treat women for ASB reduced the overall incidence of pyelonephritis from 1.83% to 0.48% ( $P < .001$ ) over a 6-year period.<sup>75</sup>

Fluoroquinolones are not recommended in pregnancy (ciprofloxacin is a Category C drug in pregnancy—"risk cannot be ruled out"), and TMP/SMX is contraindicated in the first trimester. Nitrofurantoin and fosfomycin are both Category B drugs, indicating "no evidence of risk in humans."<sup>55,56</sup>

### *Elderly Patients*

UTIs are the second most common infections among noninstitutionalized elders after respiratory tract infections. In a cohort of 417 elderly persons, UTIs accounted for 24% of all infections. Factors that predispose a postmenopausal woman to UTIs include being a nonsecretor for blood group antigens, urinary incontinence, cystoceles,

increased postvoiding residual urine, and a history of premenopausal UTIs. Institutionalized elderly individuals have a high frequency of ASB, associated primarily with comorbidities. A higher proportion of infections are polymicrobial, and there is an increased percentage of gram-positive organisms. Finally, elderly patients receive antibiotics more frequently, leading to greater likelihood of resistant pathogens.<sup>15,76</sup>

Management of UTIs in elderly persons should be conservative, using longer courses of treatment (7 to 14 days). A urine culture should be obtained prior to initiation of antimicrobial therapy. TMP/SMX may be considered a first-line agent if a resistant organism is not anticipated. Fluoroquinolones are probably appropriate where resistance is a consideration, but widespread fluoroquinolone use in some long-term care facilities has led to concerns with resistance in these populations. Although fluoroquinolones are generally very safe for elderly patients, selection of the appropriate fluoroquinolone must consider potential adverse effects. Because many elderly patients take a large number of drugs for management of chronic conditions, clinicians should consider drug interactions when any agent is added to the regimen.<sup>15</sup>

### **Managed Care Considerations**

A principal focus of managed care is to limit costs without adversely affecting clinical outcomes. The ultimate cost-benefit ratio of any treatment is difficult to calculate, since it must consider not just the acquisition cost of the drug but the potential costs of inadequate or inappropriate treatment necessitating later retreatment.

Bacterial resistance directly impacts healthcare costs as newer and more expensive therapeutic alternatives will need to be developed and used to treat patients infected with resistant bacteria.<sup>31</sup> In the case of AUC, for instance, if a patient is treated initially with a drug to which the uropathogen is resistant, the infection may not be eradicated, and the patient may need retreatment, possibly with a more expensive drug. On the other hand, if treatment is initiated with a drug to which the pathogen is susceptible, a second course of treatment—and the tests required to support that course—is generally not necessary.

Antibiotic selection in managed care is commonly based on drug cost alone, because this information is available and quantifiable, whereas the costs of inappropriate treatment are more elusive. The most important factor in determining the cost-effectiveness of an antimicrobial for AUC, however, is its effectiveness against *E coli*, the likeliest urinary pathogen.<sup>77</sup>

Managed care organizations frequently limit formularies—lists of approved drugs—to 1 or 2 in a

class, commonly based on drug cost. Clinicians are discouraged from prescribing nonformulary drugs. In one study, however, formulary restriction was significantly positively related to increased use of healthcare resources.<sup>78</sup> Another study reported that when specific guidelines limiting treatment choices were strictly enforced, the percentage of patients needing second visits for cystitis rose from 12.4% to 16.5%.<sup>79</sup>

Managed care, along with the rest of the healthcare community, has an obligation to avoid practices that may promote the emergence of pathogenic resistance. Unfortunately, some managed care initiatives may encourage inappropriate antibiotic use and may counter efforts to control resistance. These practices include promoting empiric therapy to limit diagnostic tests and avoid costs; limited time with each patient, restricting patient education about appropriate use of antibiotics; and responsiveness to patient complaints about "inadequate antibiotic use."<sup>30</sup> Managed care needs to develop comprehensive, long-range cost-control practices that also consider the impact on resistance in the larger community.

## Conclusions

The goals of therapy for AUC, as for all diseases, are resolution of clinical symptoms and limitation of recurrences, complications, and adverse treatment effects. The achievement of these goals with antimicrobial therapy is complicated by the emergence of resistance to commonly used agents. The rates of resistance against some drugs previously used as first-line therapy for AUC, notably amoxicillin and cephalosporins, limit therapeutic use of these agents. The resistance rate for TMP/SMX, the most frequently recommended drug for AUC, is now approaching 20% in some geographic areas, suggesting that it may not be reliable much longer for empiric therapy.

The implications of this resistance to antibiotics are 3-fold. First, using a drug to which pathogens may be resistant increases the likelihood of treatment failure, with consequences for patient and healthcare system costs. Second, resistant pathogens, rather than susceptible pathogens, will reproduce and colonize the host. Third, a systemic antimicrobial used for UTI may promote resistance in nonurinary pathogens, which may spread to other hosts. This is of particular concern with drugs such as the fluoroquinolones that are indicated for the treatment of many severe and life-threatening diseases.

The current IDSA guidelines recommend TMP/SMX as first-line empiric therapy for AUC, and this is often appropriate. The increasing resistance to TMP/SMX in many areas, however, makes it necessary to consider alternative agents, including fluoroquinolones, nitrofurantoin, and fosfomycin.

In a survey of primary care physicians who were asked why they prescribed a broad-spectrum antibiotic when a targeted-spectrum agent would be effective, the primary reason cited was diagnostic and treatment uncertainty.<sup>30</sup> Thus, clinicians are often inclined to follow a conservative strategy in choosing treatment.

TMP/SMX remains an appropriate first-line antibiotic for the empiric treatment of AUC. In women who have risk factors for TMP/SMX resistance or in areas where the prevalence of resistance is high, alternative agents should be considered. Alternative agents include nitrofurantoin, the fluoroquinolones, and fosfomycin. Nitrofurantoin should be considered a reasonable fluoroquinolone-sparing agent that is effective and safe for the treatment of infections caused by the most frequent urinary pathogens. In addition, nitrofurantoin is used only to treat AUC, is not systemic, and is minimally affected by resistance. This strategy provides optimal therapy for the patient while limiting potential impacts on the wider community.

## REFERENCES

1. Ronald AR, Pattullo AL. The natural history of urinary infection in adults. *Med Clin North Am.* 1991;75:299-312.
2. Johnson JR, Stamm WE. Diagnosis and treatment of acute urinary tract infections. *Infect Dis Clin North Am.* 1987;1:773-791.
3. Stamm WE. Urinary tract infections and pyelonephritis. In: Braunwald E, Fauci A, Kasper DL, eds. *Harrison's Principles of Internal Medicine.* 15th ed. New York: McGraw-Hill Medical Publishing Division; 2001.
4. Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. *Am J Med.* 2002;112:1S-10S.
5. Schappert SM. Ambulatory care visits to physician offices, hospital outpatient departments, and emergency departments: United States, 1997. *Vital Health Stat 13.* 1999;1-39.
6. Hooton TM, Scholes D, Hughes JP, et al. A prospective study of risk factors for symptomatic urinary tract infection in young women. *N Engl J Med.* 1996;335:468-474.
7. Foxman B, Barlow R, D'Arcy H, Gillespie B, Sobel JD. Urinary tract infection: self-reported incidence and associated costs. *Ann Epidemiol.* 2000;10:509-515.
8. Scholes D, Hooton TM, Roberts PL, Stapleton AE, Gupta K, Stamm WE. Risk factors for recurrent urinary tract infection in young women. *J Infect Dis.* 2000;182:1177-1182.
9. Foxman B, Geiger AM, Palin K, Gillespie B, Koopman JS. First-time urinary tract infection and sexual behavior. *Epidemiology.* 1995;6:162-168.
10. Foxman B, Frerichs RR. Epidemiology of urinary tract infection: I. Diaphragm use and sexual intercourse. *Am J Public Health.* 1985;75:1308-1313.
11. Foxman B, Frerichs RR. Epidemiology of urinary tract infection: II. Diet, clothing, and urination habits. *Am J Public Health.* 1985;75:1314-1317.
12. Fihn SD, Boyko EJ, Chen CL, Normand EH, Yarbro P, Scholes D. Use of spermicide-coated condoms and other risk factors for urinary tract infection caused by *Staphylococcus saprophyticus.* *Arch Intern Med.* 1998;158:281-287.
13. Raz R, Gennesin Y, Wasser J, et al. Recurrent urinary tract infections in postmenopausal women. *Clin Infect Dis.* 2000;30:152-156.
14. Smith HS, Hughes JP, Hooton TM, et al. Antecedent antimicrobial use increases the risk of uncomplicated cystitis in young women. *Clin Infect Dis.* 1997;25:63-68.
15. Shortliffe LM, McCue JD. Urinary tract infection at the age extremes: pediatrics and geriatrics. *Am J Med.* 2002;113:55S-66S.
16. Kunin CM. Urinary tract infections in females. *Clin Infect Dis.* 1994;18:1-10.
17. Hooton TM, Stamm WE. Diagnosis and treatment of uncomplicated urinary tract infection. *Infect Dis Clin North Am.* 1997;11:551-581.
18. McNeely SG Jr. Treatment of urinary tract infections during pregnancy. *Clin Obstet Gynecol.* 1988;31:480-487.
19. Andriole VT, Patterson TF. Epidemiology, natural history, and management of urinary tract infections in pregnancy. *Med Clin North Am.* 1991;75:359-373.
20. Krcmery S, Hromec J, Demesova D. Treatment of lower urinary tract infection in pregnancy. *Int J Antimicrob Agents.* 2001;17:279-282.
21. Stamm WE, Hooton TM. Management of urinary tract infections in adults. *N Engl J Med.* 1993;329:1328-1334.

22. Ronald A. The etiology of urinary tract infection: traditional and emerging pathogens. *Am J Med.* 2002;113(suppl 1A):14S-19S.
23. Ahmed SM, Swedlund SK. Evaluation and treatment of urinary tract infections in children. *Am Fam Physician.* Available at: <http://www.aafp.org/aafp/980401ap/ahmed2.html>. Accessed December 15, 2002.
24. Nicolle LE. Urinary tract infection in the elderly. *J Antimicrob Chemother.* 1994;33:99-109.
25. Gilstrap LC III, Lucas MJ. Urinary tract infections in women. *Curr Opin Obstet Gynecol.* 1990;2:643-648.
26. Johnson JR, Stamm WE. Urinary tract infections in women: diagnosis and treatment. *Ann Intern Med.* 1989;111:906-917.
27. Bent S, Nallamothu BK, Simel DL, Fihn SD, Saint S. Does this woman have an acute uncomplicated urinary tract infection? *JAMA.* 2002;287:2701-2710.
28. Gupta K, Hooton TM, Stamm WE. Increasing antimicrobial resistance and the management of uncomplicated community-acquired urinary tract infections. *Ann Intern Med.* 2001;135:41-50.
29. Gupta K, Hooton TM, Roberts PL, Stamm WE. Patient-initiated treatment of uncomplicated recurrent urinary tract infections in young women. *Ann Intern Med.* 2001;135:9-16.
30. Hooton TM, Levy SB. Antimicrobial resistance: a plan of action for community practice. *Am Fam Physician.* 2001;63:1087-1098.
31. Food and Drug Administration. *Highlights of FDA-21 CFR Part 201.* Published February 6, 2003.
32. Neuhauser MM, Weinstein RA, Rydman R, Danziger LH, Karam G, Quinn JP. Antibiotic resistance among gram-negative bacilli in US intensive care units: implications for fluoroquinolone use. *JAMA.* 2003;289:885-888.
33. Gupta K. Addressing antibiotic resistance. *Am J Med.* 2002;112:1S-7S.
34. Gupta K, Sahm DF, Mayfield D, Stamm WE. Antimicrobial resistance among uropathogens that cause community-acquired urinary tract infections in women: a nationwide analysis. *Clin Infect Dis.* 2001;33:89-94.
35. Gupta K, Scholes D, Stamm WE. Increasing prevalence of antimicrobial resistance among uropathogens causing acute uncomplicated cystitis in women. *JAMA.* 1999;281:736-738.
36. Karlowsky JA, Kelly LJ, Thornsberry C, Jones ME, Sahm DF. Trends in antimicrobial resistance among urinary tract infection isolates of *Escherichia coli* from female outpatients in the United States. *Antimicrob Agents Chemother.* 2002;46:2540-2545.
37. Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). *Clin Infect Dis.* 1999;29:745-758.
38. Karlowsky JA, Jones ME, Thornsberry C, Critchley I, Kelly LJ, Sahm DF. Prevalence of antimicrobial resistance among urinary tract pathogens isolated from female outpatients across the US in 1999. *Int J Antimicrob Agents.* 2001;18:121-127.
39. TSN® Database, MRL Pharmaceutical Services. Available at: <http://www.medscape.com/pages/editorial/resourcecenters/public/uti/rc-uti.ov>. Accessed December 15, 2002.
40. Goettsch W, van Pelt W, Nagelkerke N, et al. Increasing resistance to fluoroquinolones in *Escherichia coli* from urinary tract infections in the Netherlands. *J Antimicrob Chemother.* 2000;46:223-228.
41. Ena J, López-Perezaga MM, Martínez-Peinado C, Cia-Barrio MA, Ruiz-Lopez I. Emergence of ciprofloxacin resistance in *Escherichia coli* isolates after widespread use of fluoroquinolones. *Diagn Microbiol Infect Dis.* 1998;30:103-107.
42. Sahm DF, Thornsberry C, Mayfield DC, Jones ME, Karlowsky JA. Multidrug-resistant urinary tract isolates of *Escherichia coli*: prevalence and patient demographics in the United States in 2000. *Antimicrob Agents Chemother.* 2001;45:1402-1406.
43. Archer G, Polk R. Treatment and prophylaxis of bacterial infections. In: Braunwald E, Hauser S, Fauci A, eds. *Harrison's Principles of Internal Medicine.* 15th ed. New York, NY: McGraw-Hill; 2001:867-882.
44. Raz R, Chazan B, Kennes Y, et al. Empiric use of trimethoprim-sulfamethoxazole (TMP-SMX) in the treatment of women with uncomplicated urinary tract infections, in a geographical area with a high prevalence of TMP-SMX-resistant uropathogens. *Clin Infect Dis.* 2002;34:1165-1169.
45. Brown PD, Freeman A, Foxman B. Prevalence and predictors of trimethoprim-sulfamethoxazole resistance among uropathogenic *Escherichia coli* isolates in Michigan. *Clin Infect Dis.* 2002;34:1061-1066.
46. Wright SW, Wrenn KD, Haynes ML. Trimethoprim-sulfamethoxazole resistance among urinary coliform isolates. *J Gen Intern Med.* 1999;14:606-609.
47. Bactrim [package insert]. Nutley, NJ; Roche Pharmaceuticals; 2002.
48. Cipro XR [package insert]. West Haven, Conn: Bayer Corporation; 2002.
49. Kahlmeter G. The ECO•SENS Project: a prospective, multinational, multicentre epidemiological survey of the prevalence and antimicrobial susceptibility of urinary tract pathogens—interim report. *J Antimicrob Chemother.* 2000;46:15-22.
50. Gonzalez CM, Schaeffer AJ. Treatment of urinary tract infection: what's old, what's new, and what works. *World J Urol.* 1999;17:372-382.
51. Christensen B. Which antibiotics are appropriate for treating bacteriuria in pregnancy? *J Antimicrob Chemother.* 2000;46:29-34.
52. *Physicians' Desk Reference®.* 56th ed. Montvale, NJ: Medical Economics Company, Inc; 2002.
53. Sahm DF, Peterson DE, Critchley IA, Thornsberry C. Analysis of ciprofloxacin activity against *Streptococcus pneumoniae* after 10 years of use in the United States. *Antimicrob Agents Chemother.* 2000;44:2521-2524.
54. Brown PD. Antibiotic selection for urinary tract infection: new microbiologic considerations. *Curr Infect Dis Rep.* 1999;1:384-388.
55. Macrobid [package insert]. Cincinnati, Oh; Procter & Gamble Pharmaceuticals; 2002.
56. Monurol [package insert]. St Louis, Mo: Forest Pharmaceuticals, Inc; 2002.
57. Gossius G, Vorland L. A randomised comparison of single-dose vs. three-day and ten-day therapy with trimethoprim-sulfamethoxazole for acute cystitis in women. *Scand J Infect Dis.* 1984;16:373-379.
58. Pelletier LL, Michalak DP, Carter JZ, et al. A comparison of Macrobid® (nitrofurantoin monohydrate/macrocrystals) and Macrochantin® (nitrofurantoin macrocrystals) in the treatment of acute episodes of uncomplicated lower urinary tract infections. *Adv Ther.* 1992;9:32-45.
59. Bayer Pharmaceutical Division, North America. Study comparing once-daily Cipro® XR to conventional twice-daily Cipro® evaluates safety and efficacy of Cipro XR for the treatment of uncomplicated urinary tract infections. New formulation utilizes bilayer matrix of active ingredient. Available at: <http://www.bayerpharma-na.com/news/co0275.asp>. Accessed January 23, 2003.
60. Stein GE. Comparison of single-dose fosfomycin and a 7-day course of nitrofurantoin in female patients with uncomplicated urinary tract infection. *Clin Ther.* 1999;21:1864-1872.
61. Irvani A, Tice AD, McCarty JM, et al. Short-course ciprofloxacin treatment of acute uncomplicated urinary tract infection in women. The minimum effective dose. *Arch Intern Med.* 1995;155:485-494.
62. Henry DC, Nenad RC, Irvani A, et al. Comparison of sparfloxacin and ciprofloxacin in the treatment of community-acquired acute uncomplicated urinary tract infection in women. Sparfloxacin Multicenter Uncomplicated Urinary Tract Infection Study Group. *Clin Ther.* 1999;21:966-981.
63. Henry DC, Bettis RB, Riffer E, et al. Comparison of once-daily extended-release ciprofloxacin and conventional twice-daily ciprofloxacin for the treatment of uncomplicated urinary tract infection in women. *Clin Ther.* 2002;24:2088-2104.
64. Richard G, DeAbate GE, Ruoff GE, Corrado M, Fowler CL, Morgan N. A double-blind, randomized trial of the efficacy and safety of short-course, once-daily levofloxacin versus ofloxacin twice daily in uncomplicated urinary tract infections. *Infect Dis Clin Pract.* 1998;9:323-329.
65. Perry CM, Barman Balfour JA, Lamb HM. Gatifloxacin. *Drugs.* 1999;58:683-696.
66. Richard GA, Mathew CP, Kirstein JM, Orchard D, Yang JY. Single-dose fluoroquinolone therapy of acute uncomplicated urinary tract infection in women: results from a randomized, double-blind, multicenter trial comparing single-dose to 3-day fluoroquinolone regimens. *Urology.* 2002;59:334-339.
67. Irvani A, Klimberg I, Briefer C, Munera C, Kowalsky SF, Echols RM. A trial comparing low-dose, short-course ciprofloxacin and standard 7 day therapy with co-trimoxazole or nitrofurantoin in the treatment of uncomplicated urinary tract infection. *J Antimicrob Chemother.* 1999;43:67-75.
68. Stapleton A, Stamm WE. Prevention of urinary tract infection. *Infect Dis Clin North Am.* 1997;11:719-733.
69. Mavromanolakis E, Maraki S, Samonis G, Tselentis Y, Cranidis A. Effect of norfloxacin, trimethoprim-sulfamethoxazole and nitrofurantoin on fecal flora of women with recurrent urinary tract infections. *J Chemother.* 1997;9:203-207.
70. Nicolle LE, Harding GK, Thomson M, Kennedy J, Urias B, Ronald AR. Efficacy of five years of continuous, low-dose trimethoprim-sulfamethoxazole prophylaxis for urinary tract infection. *J Infect Dis.* 1988;157:1239-1242.
71. Kontiokari T, Sundqvist K, Nuutinen M, Pokka T, Koskela M, Uhari M. Randomised trial of cranberry-lingonberry juice and Lactobacillus GG drink for the prevention of urinary tract infections in women. *BMJ.* 2001;322:1571.
72. Reid G, Bruce AW. Selection of lactobacillus strains for urogenital probiotic applications. *J Infect Dis.* 2001;183:S77-S80.
73. Raz R, Stamm WE. A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. *N Engl J Med.* 1993;329:753-756.
74. Barclay L. Children with UTI need longer antibiotic course. *Medscape Pediatr.* Available at: <http://www.medscape.com/viewarticle/433329>. Accessed June 19, 2002.
75. Gratacós E, Torres PJ, Vila J, Alonso PL, Cararach V. Screening and treatment of asymptomatic bacteriuria in pregnancy prevent pyelonephritis. *J Infect Dis.* 1994;169:1390-1392.
76. Harrington RD, Hooton TM. Urinary tract infection risk factors and gender. *J Gen Specif Med.* 2000;3:27-34.
77. Rosenberg M. Pharmacoeconomics of treating uncomplicated urinary tract infections. *Int J Antimicrob Agents.* 1999;11:247-251.
78. Horn SD, Sharkey PD, Tracy DM, Horn CE, James B, Goodwin F. Intended and unintended consequences of HMO cost-containment strategies: results from the managed care outcomes project. *Am J Man Care.* 1996;2:253-264.
79. O'Connor PJ, Solberg LI, Christianson J, Amundson G, Mosser G. Mechanism of action and impact of a cystitis clinical practice guideline on outcomes and costs of care in an HMO. *Jt Comm J Qual Improv.* 1996;22:673-682.

# MANAGING ACUTE UNCOMPLICATED CYSTITIS IN THE ERA OF ANTIBIOTIC RESISTANCE



## CME CREDIT INFORMATION AND POSTTEST ASSESSMENT

Course No. EN0304 **For Primary Care Physicians, Obstetrician/Gynecologists, Urologists, and Other Healthcare Professionals Who Treat Patients With Acute Cystitis**

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 Washington School of Medicine and IMED Communications. The University of Washington School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

The University of Washington School of Medicine designates this educational activity for a maximum of 2.5 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

To apply for category 1 credit, you must:

- Complete the posttest and evaluation form
- Mail/fax your completed form to: **Continuing Medical Education  
Attn: Registrar  
University of Washington School of Medicine  
1325 Fourth Avenue  
Suite 2000  
Seattle, WA 98101  
Or fax to: 206-221-4525**

### Verification of Hours

I certify that I spent \_\_\_\_\_ hours in this CME activity as indicated by my signature below.

Signature \_\_\_\_\_

Within 2 weeks following the receipt of this form, a transcript of your category 1 hours will be mailed to you. Credit hours for this newsletter may be obtained from June 2003 through June 2005.

### POSTTEST ASSESSMENT: Please circle the correct answer.

1. The prevalence of ASB in women increases by approximately
  - a) 1% per year
  - b) 2% per year
  - c) 2% per decade
  - d) 1% per decade
2. Potential consequences of symptomatic UTI to the developing fetus are
  - a) Preterm delivery
  - b) Intrauterine growth retardation
  - c) Fetal mortality
  - d) All of the above
3. After *E coli*, the most common pathogen causing AUC is
  - a) *S saprophyticus*
  - b) *K pneumoniae*
  - c) *P mirabilis*
  - d) *Enterobacter* spp
4. A combination of signs and symptoms that points to AUC is
  - a) Dysuria, fever, flank pain, urinary frequency and urgency
  - b) Dysuria, suprapubic tenderness, urinary frequency and urgency
  - c) Dysuria, pyuria, gross hematuria, inflammation of the vulva
  - d) Dysuria, fever, suprapubic tenderness, vaginal discharge
5. Recent studies have suggested revising the level of bacteriuria defining acute uncomplicated UTI from
  - a)  $10^2$  CFU to  $\geq 10^5$  CFU/mL of urine
  - b)  $10^4$  CFU to  $\geq 10^3$  CFU/mL of urine
  - c)  $10^6$  CFU to  $\geq 10^2$  CFU/mL of urine
  - d)  $10^3$  CFU to  $\geq 10^5$  CFU/mL of urine
6. The primary cause of increasing pathogenic resistance to antimicrobials is
  - a) Prescribing an antimicrobial without correctly identifying the pathogen
  - b) Failure by the patient to complete the prescribed course of therapy
  - c) Prescribing an antimicrobial at too low a dose to eradicate the pathogen
  - d) Prescribing antimicrobials whether or not they are necessary
7. During the years 1992 to 1996, which antimicrobials were associated with the highest rates of resistance in *E coli* causing AUC?
  - a) Ampicillin, cephalothin, ciprofloxacin
  - b) Cephalothin, ciprofloxacin, nitrofurantoin
  - c) Ampicillin, cephalothin, TMP/SMX
  - d) Ampicillin, cephalothin, nitrofurantoin
8. The strongest risk factor for predicting resistance to TMP/SMX is
  - a) Diabetes
  - b) Current use of any antibiotic
  - c) Hospitalization
  - d) Recent use of TMP/SMX
9. Strategies to prevent RUTI that have met with some success are
  - a) Pharmacologic, eg, prophylaxis with an antimicrobial
  - b) Nonpharmacologic, eg, drinking cranberry juice
  - c) Behavioral, eg, self-diagnosis and patient-initiated treatment
  - d) All of the above
10. An issue of concern with regard to increasing resistance to antimicrobials is
  - a) Increased likelihood of treatment failure
  - b) Increased likelihood of recurrence
  - c) Potential for selecting for resistant pathogens in the patient
  - d) All of the above

**Please record your posttest answers on the other side.**

**POSTTEST ANSWERS**

Please record your posttest answers:

1. \_\_\_\_ 2. \_\_\_\_ 3. \_\_\_\_ 4. \_\_\_\_ 5. \_\_\_\_ 6. \_\_\_\_ 7. \_\_\_\_ 8. \_\_\_\_ 9. \_\_\_\_ 10. \_\_\_\_

**EVALUATION FORM**

We would appreciate your answers to the following questions in order to help us plan for future activities of this type.

1. How would you rate: (please ✓)    Excellent    Good    Fair    Poor
- a. Value of the topic                    \_\_\_\_\_
  - b. Relevance to your practice        \_\_\_\_\_
  - c. Organization of monograph        \_\_\_\_\_
  - d. Publication length                    \_\_\_\_\_
  - e. Quality of information                \_\_\_\_\_

2. Were the goals and objectives clearly stated and achieved?  
 Yes     No
3. Will reading this newsletter change the way in which you manage patients?  
 Yes     No  
 Please be as specific as possible: \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

4. How do you prefer to receive continuing medical education information?  
 (On a scale of 5 to 1, please score each of the following:  
 5 = very useful; 3 = somewhat useful; 1 = don't use.)
- \_\_\_\_\_ a. Newsletter                    \_\_\_\_\_ f. Journal articles/supplements
  - \_\_\_\_\_ b. Videotape                    \_\_\_\_\_ g. Symposium/conference
  - \_\_\_\_\_ c. Audiotape/audio CD        \_\_\_\_\_ h. CD-ROM/video
  - \_\_\_\_\_ d. Teleconference                \_\_\_\_\_ i. Internet
  - \_\_\_\_\_ e. Monograph

5. How did you hear about this program?
- \_\_\_\_\_ a. Direct mail                    \_\_\_\_\_ e. Colleague
  - \_\_\_\_\_ b. Announcement card        \_\_\_\_\_ f. Other: \_\_\_\_\_
  - \_\_\_\_\_ c. OWH/DHHS website            \_\_\_\_\_
  - \_\_\_\_\_ d. Medscape link                    \_\_\_\_\_

6. In your opinion, was the information in this newsletter biased toward any commercial product or service?  
 Yes     No  
 If yes, please comment: \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

7. Do you believe such materials, supported by educational grants from industry, are:  
 10 very appropriate/useful, 0 not appropriate/useful? \_\_\_\_\_

8. Additional comments and/or suggested topics for future CME activities:  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

First Name (please print) \_\_\_\_\_

Last Name \_\_\_\_\_ Degree \_\_\_\_\_

Specialty \_\_\_\_\_

Street Address \_\_\_\_\_

City \_\_\_\_\_ State \_\_\_\_\_ ZIP \_\_\_\_\_

Business Phone \_\_\_\_\_ Home Phone \_\_\_\_\_

Fax \_\_\_\_\_ E-mail Address \_\_\_\_\_

**For additional continuing medical education opportunities related to this subject, visit  
The Office on Women's Health of the U.S. Department of Health and Human Services website at:  
[www.4woman.gov/healthpro/contedu](http://www.4woman.gov/healthpro/contedu)**

*CLINICIAN*<sup>®</sup> publishes medical data arising out of scientific meetings or submitted as papers forming the theme of a monograph on contemporary therapeutics. The publishers reserve copyright and renewal on all published material. Any such material may not be reproduced in any form without the written permission of IMED Communications.

The opinions expressed in *CLINICIAN*<sup>®</sup> are those of the contributing faculty and do not necessarily reflect the view or policies of the University of Washington, School of Medicine, The Office on Women's Health of the U.S. Department of Health and Human Services, the American Academy of Nurse Practitioners, the American College of Nurse Midwives, the American Medical Association, the National Association of Managed Care Physicians, the Society for Women's Health Research, IMED Communications, or the program grantor, Procter & Gamble Pharmaceuticals, Inc. Full prescribing information must be consulted on any of the drugs or procedures described herein. This material is prepared based on a review of multiple sources of information, but is not exhaustive of the subject matter. Therefore, healthcare professionals and other individuals should review and consider other publications and materials on the subject matter before relying solely on the information contained within this material.

**All correspondence concerning the contents  
of this publication should be directed to:**

**The Editor, *CLINICIAN*<sup>®</sup>  
IMED Communications  
518 Route 513, Dept. 115  
Suite 200  
PO Box 458  
Califon, NJ 07830**



Developed and Produced by



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



In cooperation with  
AANP, APUA, ACNM, AMA, NPWH, NAMCP, SWHR

This program is supported by an educational grant from Procter & Gamble Pharmaceuticals, Inc. 