Acute Uncomplicated Cystitis in an Era of Increasing Antibiotic Resistance: A Proposed Approach to Empirical Therapy

Thomas M. Hooton,[1] Richard Besser,[2] Betsy Foxman,[3] Thomas R. Fritsche,[4] and Lindsay E. Nicolle[5]

[1]University of Washington, Seattle; [2]Centers for Disease Control and Prevention, Atlanta, Georgia; [3]University of Michigan, Ann Arbor; [4]The Jones Group/JMI Laboratories, North Liberty, Iowa; and [5]University of Manitoba, Winnipeg, Canada

Acute uncomplicated lower urinary tract infection (cystitis) is one of the most common and easily cured bacterial infections in women. However, increasing antibiotic resistance complicates its treatment by increasing patient morbidity, costs of reassessment and retreatment, rates of hospitalization, and use of broader-spectrum antibiotics. Guidelines published in 1999 by the Infectious Diseases Society of America (IDSA) recommend trimethoprim-sulfamethoxazole (TMP-SMX) as first-line treatment for acute cystitis—noting, however, that resistance to this agent is increasing [1]. Although public health authorities have increasingly recommended narrow-spectrum antibiotics for treating community-acquired respiratory and urinary tract infections (UTIs) whenever possible, concerns about resistance have resulted in a burgeoning use of fluoroquinolones. In the past few years, use of fluoroquinolones (overall and for UTIs) in ambulatory care has dramatically increased, whereas use of TMP-SMX for UTIs has decreased [2–4]. If trends in the use of fluoroquinolones continue, this crucial class of drugs is likely to become less effective, not only for treating respiratory and urinary tract infections, but also for treating foodborne infections, sexually transmitted diseases, and health care–associated infections.

Prompted, in part, by the well-documented increase in the use of fluoroquinolones for treating upper respiratory tract infections and the evolving resistance of uropathogens to TMP-SMX, the Alliance for the Prudent Use of Antibiotics convened a scientific meeting of experts on 10 June 2003 to review current knowledge of the epidemiology of uncomplicated UTIs, examine the adequacy of the current treatment guidelines, discuss options to improve empiric UTI treatment and minimize antimicrobial resistance, and consider how resistance should be factored into the development of professional guidelines for treatment of UTIs. This report summarizes the discussion and findings from this meeting.

Received 9 January 2004; accepted 20 April 2004; electronically published 14 June 2004.

This report is based on a meeting organized by the Alliance for the Prudent Use of Antibiotics (APUA) in Boston, Massachusetts, on 10 June 2003. Conference participants are listed at the end of the text.

The views expressed in this publication do not necessarily reflect the official positions of the Centers for Disease Control and Prevention, the Department of Health and Human Services, or the APUA.

Reprints or correspondence: Dr. Thomas M. Hooton, Harborview Medical Center, 325 Ninth Ave., Box 359930, Seattle, WA 98104-2499 (hooton@u.washington.edu).

Clinical Infectious Diseases 2004; 39:75–80

1058-4838/2004/3901-0013$15.00

BACKGROUND

Epidemiology. Acute uncomplicated cystitis, which is characterized by dysuria, frequent and/or urgent urination, bacteriuria, and pyuria, occurs primarily in healthy, premenopausal, nonpregnant adult women with apparently normal urinary tracts. By the age of 24 years, 1 in 3 women has experienced ⩾1 episode, and it is estimated that as many as 60% of women report having had a UTI in their lifetime [5, 6]. The peak incidence of disease occurs during the sexually active years, between 18–39 years of age [7]. Approximately 30%–40% of patients will experience ⩾1 recurrence [8, 9]. Although morbidity may be low compared with that of other diseases, the impact is substantial. Each episode of cystitis in female college students has been associated with a mean of 6.1 symptomatic days and a mean of 2.4 days of restricted activity [5]. Annual direct and indirect costs for community-acquired UTI were estimated to approach $2 billion in 1995 [5, 6].

The microbiological findings associated with acute uncomplicated cystitis are highly consistent: 80%–85% of episodes are caused by *Escherichia coli*, and ~5%–15% are caused by *Staphylococcus saprophyticus. Klebsiella pneumoniae, Proteus mirabilis,* group B streptococci, and other uropathogens occur in small numbers. Uropathogens are assumed to originate primarily from the bowel flora, although other potential reservoirs have not been well studied.

Several behavioral factors are associated with acute uncomplicated cystitis. The most important are recent vaginal intercourse and spermicide use, especially in conjunction with diaphragm use [10, 11]. Nonsecretors of ABH blood-group antigens have an increased risk of recurrent UTI, compared with secretors [12]. The increased risk appears to be associated with the expression of certain cell surface glycosphingolipids that bind with greater avidity to *E. coli* and are not found in secretors [13].

Resistance trends. During the past 2 decades, antimicrobial resistance among community-acquired uropathogens has increased. Before 1990, resistance to TMP-SMX was 0%–5% [14]. By the early-to-mid 1990s, studies were reporting that 7%–18% of *E. coli* strains causing cystitis were resistant to TMP-SMX [14, 15]. In a nationwide surveillance study of urinary *E. coli* from female outpatients in the United States, the prevalence of TMP-SMX resistance was 15% in 1995, 17% in 1998, and 16% in 2001 [16]. Of note, data for this study were collected from hospital laboratories without regard to patient diagnostic or prescription history. A European survey of a well-defined population of women with acute uncomplicated cystitis (the ECO-SENS Project, conducted during 1999–2000) found TMP-SMX resistance in 9%–15% of *E. coli* in all countries except Spain and Portugal, where the rate was nearly 35% [17].

TMP-SMX resistance has been associated with concurrent resistance to other recommended UTI antibiotics [18]. *E. coli* strains resistant to TMP-SMX, for example, are 14 times more likely to be resistant to ciprofloxacin than are susceptible *E. coli* strains (9.5% vs. 0.7%), and they are 4 times more likely to be resistant to nitrofurantoin (1.9% vs. 0.5%) [19]. Despite this cross-resistance, the vast majority of TMP-SMX–resistant strains are susceptible to $\geqslant$1 alternative agents used for treating UTI.

Available resistance surveillance programs vary with respect to the source of data and how data are filtered; thus, some resistance prevalence data may be questionable. Current surveillance estimates are potentially skewed by 2 potential biases that can overestimate the prevalence of resistance in a community. One bias is culture selection: outpatients whose UTIs are serious, recurrent, do not respond to empirical therapy, or require hospitalization are more likely to have cultures performed. These are also patients with a greater likelihood of being infected with resistant *E. coli.* The other potential bias is sample selection: surveillance that draws on hospital laboratories is more likely to reflect inpatients, sicker patients, and patients with complicated UTI. Bacteria causing complicated UTI are more likely to be resistant to antibiotics, compared with bacteria causing uncomplicated cystitis [20].

Local antibiograms, which primarily reflect clinicians' experiences with the treatment of patients experiencing complications, distort the true resistance picture and skew decisions about therapeutic choices. With such antibiograms, it is often not possible to obtain site-specific pathogen resistance data; for example, *E. coli* may be represented by strains associated with urinary, respiratory, and wound infections. As a result, appropriate susceptibility data for the selection of empirical therapy are seldom accessible.

UTI treatment guidelines. The 1999 IDSA guidelines recommend treatment with TMP-SMX (or TMP alone) for 3 days as standard therapy for acute uncomplicated cystitis [1]. Other recommended treatments include a 3-day regimen of fluoroquinolones (e.g., ciprofloxacin, norfloxacin, and ofloxacin—gatifloxacin and levofloxacin are alternatives not mentioned in the guidelines); a 7-day regimen of nitrofurantoin; and single-dose treatment with fosfomycin tromethamine. Fluoroquinolones are not recommended as initial empirical therapy unless the prevalence of TMP-SMX or TMP resistance among local strains of *E. coli* exceeds 10%–20%, although this prevalence range is a suggested threshold and is not based on evidence.

Another agent—the older, narrow-spectrum drug nitrofurantoin—has led to little resistance among *E. coli,* but it may have lower cure rates (85%), compared with those of other first-line agents (90%–95%), and more side effects, especially acute and chronic pulmonary syndromes [1]. The limited data available for fosfomycin also suggest lower cure rates and more side effects [1]. According to the guidelines, nitrofurantoin and fosfomycin therapy may become more useful as resistance to TMP-SMX and TMP increases, but they require further study [1].

There are numerous other UTI treatment guidelines worldwide, with TMP-SMX generally listed as the drug of choice for first-line therapy [21–23]. However, widely varying prescription practices suggest that guidelines are not uniformly followed, even in developed countries [4, 24]. Patient characteristics (e.g., age, race, and symptoms) and physician specialty influence treatment choice [4]. Other forces partly responsible for variability in antimicrobial use include differences in regulatory approval, marketing pressures, reimbursement policies, and individual practice experience [25] . Thus, although the IDSA guidelines summarize scientific thinking and may influence insurance benefits coverage, they appear to have limited influence on individual clinical practice [25].

The campaign by the Centers for Disease Control and Prevention (CDC; Atlanta, GA) to reduce unnecessary antibiotic prescriptions for upper respiratory tract infections (many of which are caused by viruses) [26] may be relevant to the treatment of acute cystitis. Beginning in 1995, the CDC undertook a broad-based effort to change prescribing patterns by first identifying why health care professionals prescribed antimicrobial agents inappropriately and then intervening to promote more prudent decisions. The CDC established partnerships with managed care organizations, pharmacy benefit

management companies, pharmaceutical companies, large health care purchasers, medical schools, and professional societies to communicate the message to physicians and the public. The CDC has also initiated active population-based surveillance and enhanced passive surveillance of resistance trends, and it has supported such practices as physician profiling to raise individual awareness of prescribing habits. This comprehensive approach has been linked with a decrease in overall use of antibiotics [27, 28]. However, because UTIs are primarily bacterial in origin, interventions must focus more on appropriate antibiotic choice and duration of therapy than on limiting the number of prescriptions for antibiotics.

A PROPOSED APPROACH TO EMPIRICAL THERAPY

TMP-SMX and TMP have long been considered to be first-line agents for the treatment of uncomplicated cystitis and should remain so [1]. They are highly effective for treating this condition, well-tolerated, and inexpensive. However, recent studies have demonstrated that the use of TMP-SMX for treating cystitis is decreasing and that the use of fluoroquinolones is increasing. Most studies show similar treatment outcomes for patients treated with TMP-SMX and those treated with fluoroquinolones, although these trials have not included large numbers of women infected with TMP-SMX–resistant uropathogens. Yet the increased use of fluoroquinolones for cystitis may spawn wider resistance and thus undermine treatment of other types of infections. Although no published studies have reported that short-course fluoroquinolone therapy for acute uncomplicated cystitis selects for fluoroquinolone-resistant flora, selection for fluoroquinolone-resistant rectal *E. coli* has been reported in other patient groups (e.g., after single-dose prophylaxis in men undergoing urologic procedures [29] and after 28-day treatment for prostatitis [30]). Given concerns about fluoroquinolone resistance, a greater emphasis should be placed on the use of nonfluoroquinolone drugs for the treatment of acute uncomplicated cystitis—at least for less-severe infections—when TMP-SMX is not an option.

What nonfluoroquinolone drugs, then, are appropriate choices for treating uncomplicated cystitis? Nitrofurantoin is restricted to treating or preventing uncomplicated cystitis, and resistance in *E. coli* is very low even after 50 years of use. In addition, the use of nitrofurantoin is unlikely to lead to cross-resistance to those antimicrobials that are used to treat other important infections. There is, however, insufficient evidence to demonstrate that 3-day regimens of nitrofurantoin are as effective as 3-day regimens of TMP-SMX or fluoroquinolones [1]. Some clinicians are concerned that the recommended 7-day regimen may lead to a lack of patient compliance, and there are safety concerns as well, although the frequency of major adverse reactions has been shown to be exceptionally low [31]. Despite the remarkable in vitro activity of nitrofurantoin against urinary *E. coli,* a large study of women with acute uncomplicated cystitis reported that 6%–9% of isolates annually and 41% of all non–*E. coli* isolates recovered from 1992 through 1996 were resistant to this agent [15]. In addition, Karlowsky et al. [19] have pointed out that 10.4% of ciprofloxacin-resistant isolates were resistant to nitrofurantoin and that 29.8% of the nitrofurantoin-resistant isolates were resistant to ciprofloxacin. Thus, it is conceivable that increasing use of either fluoroquinolones or nitrofurantoin will select for resistance to both—underscoring the need for drug susceptibility surveillance [19]. On balance, however, nitrofurantoin should be given more emphasis as a fluoroquinolone-sparing, second-line agent when TMP-SMX cannot be used in women with mild-to-moderate episodes of uncomplicated cystitis in whom treatment failure is likely to have minor consequences.

Single-dose fosfomycin treatment is significantly less effective in eradicating bacteriuria than is TMP-SMX therapy for 10 days or ciprofloxacin therapy for 7 days [32]. Moreover, in a meta-analysis of 2 trials in which single-dose fosfomycin was compared with multiday regimens of norfloxacin, fosfomycin was found to have similar eradication and recurrence rates but a significantly higher rate of adverse events [1]. Therefore, fosfomycin is not recommended for first-line treatment of cystitis, but it is a reasonable alternative to fluoroquinolones for treating mild episodes of acute uncomplicated cystitis when TMP-SMX is not an option.

Although β-lactam antibiotics are often used for treating acute cystitis, they have been found to be less effective than TMP-SMX and fluoroquinolones in comparative trials and are generally not recommended as first-line treatment for cystitis [1, 32, 33]. Later-generation oral agents (e.g., cefpodoxime) may perform better, but published data are sparse [34]. Further study is warranted to determine how β-lactams compare with nitrofurantoin and fosfomycin as second-line treatment regimens.

TMP-SMX therapy is the least expensive treatment option, and fosfomycin therapy is the most costly. The cost of the currently recommended 7-day regimen of nitrofurantoin lies between that of TMP-SMX and fosfomycin and is about the same as that of fluoroquinolones [35]. Of note, generic formulations of nitrofurantoin and ciprofloxacin are expected soon. Although fluoroquinolones are more expensive than TMP-SMX, the cost differential may not be significant in practice when factoring in expenses associated with treatment failures and adverse events [32]. On the other hand, there is a need to limit emerging resistance to the fluoroquinolone class of drugs.

Treatment choice should also be informed by an understanding of the natural course of cystitis. It has been assumed that high urinary levels of drugs are associated with cure, even when treating infections due to resistant isolates. In recent trials, however, ~50% of patients treated with TMP-SMX and infected with resistant or-

ganisms experienced bacteriologic failure, and 40% experienced clinical failure [32]. The natural history of UTI is, in fact, resolution in ~50% of episodes after 2–4 weeks [36, 37]. Thus, the response in patients infected with resistant organisms may simply reflect the expected spontaneous resolution of infection with nontreatment.

What, then, should be the threshold for moving from empirical TMP-SMX to empirical fluoroquinolones or other drugs? Concern about resistance drives clinicians to use broader-spectrum agents, such as fluoroquinolones, for empirical first-line therapy. Indeed, with no resistance to TMP-SMX, there is a predicted 93% bacteriologic eradication rate and a 95% clinical cure rate when TMP-SMX is used; but even with a 30% rate of resistance to TMP-SMX, the bacteriologic eradication rate is predicted to be 80%, and the clinical cure rate is predicted to be 85% [18]. In other words, even with rates of resistance greater than those seen in current clinical practice, the clinical cure rate is high—a fact that supports the continued use of TMP-SMX as first-line empirical therapy [18].

Although surveillance data reflect population-wide resistance trends, clinicians need to be able to predict TMP-SMX resistance in individual patients. Reported risk factors for infection with a TMP-SMX–resistant strain include recent hospitalization, diabetes, current use of antibiotics, and use of TMP-SMX within the previous 3 months [38]. It is therefore reasonable for clinicians to factor such information into their patient assessments to help determine when TMP-SMX should be avoided. It is not clear whether recent use of other agents predicts resistance to such antibiotics in subsequent UTIs, but it seems reasonable to factor this information into empirical treatment decisions.

To summarize, clinicians currently face dilemmas in determining empirical therapy for cystitis. They can choose either TMP-SMX, despite concerns of increasing resistance; somewhat less effective and more-expensive antibiotics without other clinical uses and with little or no cross-resistance (nitrofurantoin and fosfomycin); or fluoroquinolones, with the potential for increasing community resistance—a major public health concern. With higher levels of TMP-SMX resistance in uropathogens and the increasingly widespread use of fluoroquinolones for common community infections, the panel suggests that UTI treatment guidelines need to be clarified and refined. Though this is optimally achieved through appropriate clinical trials, relevant studies are often not available. An updated approach to empirical treatment of acute uncomplicated cystitis has been proposed that is based on current knowledge of this disease and on recent trends in antimicrobial resistance (see Appendix).

CONCLUSIONS AND RECOMMENDATIONS

- Fluoroquinolones are excellent drugs and have an important role in treating uncomplicated cystitis—but not as first-line therapy. Increasing fluoroquinolone resistance is a serious public health threat, and it is essential that we avoid using these agents indiscriminately if we are to preserve the efficacy of these critical drugs. The routine use of fluoroquinolones for treating mild-to-moderate acute uncomplicated cystitis should be discouraged.
- Current surveillance systems likely exaggerate the prevalence of resistance among community-acquired uropathogens because of culture-selection bias and dependence on data from hospital settings. Clinicians need resistance estimates that are based on data gathered from primary care clinics and offices, school-based clinics, and university clinics. Such data, however, are seldom available.
- Increasing—and possibly exaggerated—estimates of resistance to TMP-SMX are leading clinicians to replace this inexpensive and effective drug with fluoroquinolones for the treatment of acute uncomplicated cystitis. Fluoroquinolone-sparing agents should be given higher priority in the treatment of this infection. Researchers should study the efficacy of courses of nitrofurantoin that are shorter than the currently recommended 7 days.
- Professional societies need to assist clinicians in applying observations from resistance prevalence surveys to clinical practice.
- Current Infectious Diseases Society of America guidelines should be updated to address the appropriate use of second-line agents and clarified with regard to use of fluoroquinolones. Guideline development should incorporate not only concerns about resistance rates, but also concerns about the unnecessary use of broad-spectrum agents when more-targeted therapy is reliable. Such revised guidelines should be tested in practice to determine their efficacy.

CONFERENCE PARTICIPANTS

Dr. Thomas M. Hooton, University of Washington (Chair); Dr. Richard Besser, Centers for Disease Control and Prevention; Dr. George M. Eliopoulos, Beth Israel Deaconess Medical Center, Harvard Medical School; Dr. Betsy Foxman, University of Michigan; Dr. Thomas R. Fritsche, The Jones Group/JMI Laboratories; and Dr. Lindsay E. Nicolle, University of Manitoba.

Alliance for the Prudent Use of Antibiotics staff. Kathleen Young and Dr. Barbara A. Souder.

Alliance for the Prudent Use of Antibiotics program coordinators. Stefanie Valovic and Tarah Farman.

Acknowledgments

We would like to thank the Alliance for the Prudent Use of Antibiotics, for organizing the meeting, and Kathy Young, Anibal Sosa, Stefanie Valovic, Bonnie Marshall, and Madeline Drexler, for help in preparing this manuscript.

Financial support. The Alliance for the Prudent Use of Antibiotics.

Conflict of interest. T.M.H. has served as a consultant to Bayer and to Procter and Gamble Pharmaceutical and has received honoraria from Bayer, Bristol-Myers Squibb, and Ortho-McNeil Pharmaceutical. B.F. has served as an expert consultant for Bayer and Ocean Spray and has received an unrestricted educational grant from Pfizer. T.F. has served on an advisory board for Novartis Pharmaceuticals and has consulted for Abbott Laboratories and Ortho-McNeil Pharmaceutical. L.N. is a consultant and lecturer for Proctor and Gamble and Leo Pharmaceuticals, has received grant funding from MedImmune, and has lectured for and received grant funding from Bayer. R.B.: No conflict.

APPENDIX

A PROPOSED APPROACH TO THE EMPIRICAL TREATMENT OF ACUTE UNCOMPLICATED CYSTITIS

Trimethoprim-sulfamethoxazole (TMP-SMX) or trimethoprim should be first-line treatment for women who:

- have no history of allergy to the drug AND
- have had no antibiotic treatment (especially TMP-SMX treatment) in the previous 3 months AND
- have had no recent hospitalization AND
- live in communities in which the prevalence of *Escherichia coli* resistance to TMP-SMX is not known to be ⩾20% in women with acute uncomplicated cystitis.

Nitrofurantoin should be encouraged as a fluoroquinolone-sparing agent for women who have mild to moderate symptoms AND:

- allergy to TMP-SMX, OR
- antibiotic treatment in previous 3 months (except for nitrofurantoin treatment) OR
- live in communities in which the prevalence of *E. coli* resistance to TMP-SMX is known to be ⩾20% in women with acute uncomplicated cystitis.

Fosfomycin should be encouraged as a fluoroquinolone-sparing agent for women who have mild symptoms AND:

- allergy to TMP-SMX, OR
- antibiotic treatment in the previous 3 months (except for fosfomycin treatment) OR
- live in communities in which the prevalence of *E. coli* resistance to TMP-SMX is known to be ⩾20% in women with acute uncomplicated cystitis.

A fluoroquinolone should be considered for women who have severe symptoms AND:

- allergy to TMP-SMX OR
- antibiotic treatment in previous 3 months (except for fluoroquinolone treatment) OR
- live in communities in which the prevalence of *E. coli* resistance to TMP-SMX is known to be ⩾20% in women with acute uncomplicated cystitis.

References

1. Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Clin Infect Dis **1999**; 29:745–58.
2. McCaig LF, Besser RE, Hughes JM. Antimicrobial-drug prescription in ambulatory care settings, United States, 1992–2000. Emerg Infect Dis **2003**; 9:432–7.
3. Steinman MA, Gonzales R, Linder JA, Landefeld CS. Changing use of antibiotics in community-based outpatient practice, 1991–1999. Ann Intern Med **2003**; 138:525–33.
4. Huang ES, Stafford RS. National patterns in the treatment of urinary tract infections in women by ambulatory care physicians. Arch Intern Med **2002**; 162:41–7.
5. Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. Am J Med **2002**; 113:5S–13S.
6. Foxman B, Barlow R, D'Arcy H, Gillespie B, Sobel JD. Urinary tract infection: self-reported incidence and annual costs. Ann Epidemiol **2000**; 10:509–14.
7. Centers for Disease Control and Prevention. Third national health and nutrition examination survey (NHANES III) public-use data files. Available at: http://www.cdc.gov/nchs/products/elec_prods/subject/nhanes3.htm. Accessed 23 May 2004.
8. Foxman B, Gillespie B, Koopman J, et al. Risk factors for second urinary tract infection among college women. Am J Epidemiol **2000**; 151:1194–205.
9. Ikaheimo R, Siitonen A, Heiskanen T, et al. Recurrence of urinary tract infection in a primary care setting: analysis of a 1-year follow-up of 179 women. Clin Infect Dis **1996**; 22: 91–9.
10. Foxman B. Recurring urinary tract infection: incidence and rising risk factors. Am J Pub Health **1990**; 80:331–3.
11. 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**; 335:468–74.
12. Sheinfeld, J, Schaeffer AJ, Cordon-Cardo C, Rogatko A, Fair WR. Association of the Lewis blood-group phenotype with recurrent urinary tract infections in women. N Engl J Med **1989**; 320:773–7.
13. Stapleton AE, Stroud MR, Hakomori SI, Stamm WE. The globoseries glycosphingolipid sialosyl galactosyl globoside is found in urinary tract tissues and is a preferred binding receptor in vitro for uropathogenic *Escherichia coli* expressing pap-encoded adhesins. Infect Immun **1998**; 66:3856–61.
14. Gupta K. Emerging antibiotic resistance in urinary tract pathogens. Infect Dis Clin North Am **2003**; 17:243–59.
15. Gupta K, Scholes D, Stamm WE. Increasing prevalence of antimicrobial resistance among uropathogens causing acute uncomplicated cystitis in women. JAMA **1999**; 281:736–8.
16. 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**; 46:2540–5.
17. 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(Suppl 1):15–22.
18. 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.
19. Karlowsky JA, Thornsberry C, Jones ME, Sahm DF. Susceptibility of antimicrobial-resistant urinary *Escherichia coli* isolates to fluoroquinolones and nitrofurantoin. Clin Infect Dis **2003**; 36:183–7.
20. Nicolle LE. A practical guide to the management of complicated urinary tract infection. Drugs **1997**; 53:583–92.
21. Urinary Tract Infection Guideline Team. University of Michigan health system urinary tract infection guideline, June **1999**. Available at: http://www.cme.med.umich.edu/pdf/guideline/UTI.pdf. Accessed 23 May 2004.
22. Institute for Clinical Systems Improvement health care guideline: uncomplicated urinary tract infection in women. November **2002**.

Updated 3 January 2003. Available at:http://www.icsi.org/knowledge/index.asp. Accessed 9 June 2004.
23. Smith MBH. Screening for urinary infection in asymptomatic infants and children. In: Canadian Task Force on the Periodic Health Examination. Canadian guide to clinical preventive health care. Ottawa: Health Canada, **1994**: 220–30.
24. Naber KG. Survey on antibiotic usage in the treatment of urinary tract infections. J Antimicrob Chemother **2000**; 46(Suppl 1):49–52.
25. McEwen LN, Farjo R, Foxman B. Antibiotic prescribing for cystitis: how well does it match published guidelines? Ann Epidemiol **2003**; 13:479–83.
26. Gonzales R, Bartlett JG, Besser RE, et al. Principles of appropriate antibiotic use for treatment of acute respiratory tract infections in adults: background, specific aims, and methods. Ann Intern Med **2001**; 134:479–86.
27. Emmer CL, Besser RE. Combating antimicrobial resistance: intervention programs to promote appropriate antibiotic use. Infect Med **2002**; 19:160–73.
28. McCaig LF, Besser RE, Hughes JM. Trends in antimicrobial prescribing rates for children and adolescents. JAMA **2002**; 287:3096–102.
29. Wagenlehner F, Stower-Hoffman J, Schneider-Brachert W, Naber KG, Lehn N. Influence of a prophylactic single dose of ciprofloxacin on the level of resistance of *Escherichia coli* to fluoroquinolones in urology. Int J Antimicrob Agents **2000**; 15:207.
30. Horcajada JP, Vila J, Moreno-Martinez A, et al. Molecular epidemiology and evolution of resistance to quinolones in *Escherichia coli* after prolonged administration of ciprofloxacin in patients with prostatitis. J Antimicrob Chemother **2002**; 49:55.
31. Guay DR. An update on the role of nitrofurans in the management of urinary tract infections. Drugs **2001**; 61:353–64.
32. Hooton TM. The current management strategies for community-acquired urinary tract infection. Infect Dis Clin North Am **2003**; 17: 303–32.
33. Nicolle LE. Urinary tract infection: traditional pharmacologic therapies. Am J Med **2002**; 113: 35S–44S.
34. Goto T, Kitagawa T, Kawahara M, Hayami H, Ohi Y. Comparative study of single-dose and three-day therapy for acute uncomplicated cystitis. Hinyokika Kiyo **1999**; 45:85–9.
35. Fosfomycin for urinary tract infections. Med Lett Drugs Ther **1997**; 39:66–8.
36. Nicolle LE. Pivmecillinam in the treatment of urinary tract infections. J Antimicrob Chemother **2000**; 46(Suppl 1):35–9.
37. Christiaens TC, De Meyere M, Verschraegen G, Peersman W, Heytens S, De Maeseneer JM. Randomized controlled trial of nitrofurantoin versus placebo in the treatment of uncomplicated urinary tract infection in adult women. Br J Gen Pract **2002**; 52:708–10.
38. Wright SW, Wrenn KD, Haynes ML. Trimethoprim-sulfamethoxazole resistance among urinary coliform isolates. J Gen Intern Med **1999**;14:606–9.