REVIEW ARTICLE

Drugs 2008; 68 (9): 1169-1205
0012-6667/08/0009-1169/$53.45/0

© 2008 Adis Data Information BV. All rights reserved.

Contemporary Management of Uncomplicated Urinary Tract Infections

David R.P. Guay

Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota, USA

Contents

Abstract

Uncomplicated urinary tract infections (uUTIs) are common in adult women across the entire age spectrum, with mean annual incidences of approximately 15% and 10% in those aged 15–39 and 40–79 years, respectively. By definition, UTIs in males or pregnant females and those associated with risk factors known to increase the risk of infection or treatment failure (e.g. acquisition in a hospital setting, presence of an indwelling urinary catheter, urinary tract instrumentation/interventions, diabetes mellitus or immunosuppression) are not considered herein.

The majority of uUTIs are caused by *Escherichia coli* (70–95%), with *Proteus mirabilis*, *Klebsiella* spp. and *Staphylococcus saprophyticus* accounting for 1–2%, 1–2% and 5–10% of infections, respectively. If clinical signs and symptoms consistent with uUTI are present (e.g. dysuria, frequency, back pain or

costovertebral angle tenderness) and there is no vaginal discharge or irritation present, the likelihood of uUTI is >90–95%. Laboratory testing (i.e. urinary nitrites, leukocyte esterase, culture) is not necessary in this circumstance and empirical treatment can be initiated.

The ever-increasing incidence of antimicrobial resistance of the common uropathogens in uUTI has been and is a continuing focus of intensive study. Resistance to cotrimoxazole (trimethoprim/sulfamethoxazole) has made the empirical use of this drug problematic in many geographical areas. If local uropathogen resistance rates to cotrimoxazole exceed 10–25%, empirical cotrimoxazole therapy should not be utilized (fluoroquinolones become the new first-line agents). In a few countries, uropathogen resistance rates to the fluoroquinolones now exceed 10–25%, rendering empirical use of fluoroquinolones problematic. With the exception of fosfomycin (a second-line therapy), single-dose therapy is not recommended because of suboptimal cure rates and high relapse rates. Cotrimoxazole and the fluoroquinolones can be administered in 3-day regimens. Nitrofurantoin, a second-line therapy, should be given for 7 days. β-Lactams are not recommended because of suboptimal clinical and bacteriological results compared with those of non-β-lactams. If a β-lactam is chosen, it should be given for 7 days.

Management of uUTIs can frequently be triaged to non-physician healthcare personnel without adverse clinical consequences, resulting in substantial cost savings. It can be anticipated that the optimal approach to the management of uUTIs will change substantially in the future as a consequence of antimicrobial resistance.

Urinary tract infections (UTIs) account for at least 7 million outpatient visits and 1 million (or 1%) hospital admissions annually in the US, with total costs exceeding $US1 billion (year of costing not stated).[1] Up to 15% of women develop UTIs each year and over 25% will have one or more recurrences.[2]

In a survey of 2000 adult women in the US, 11% reported at least one UTI during the previous year (highest prevalence was 17.5% in 18- to 24-year-olds). By age 26 years, one-third of women had experienced at least one UTI during the previous year. Lifetime incidence of UTI in adult women was 60%. In college-age women, the UTI incidence was 0.5–0.7 episodes per person-year, while in 55- to 75-year-old postmenopausal women it was 0.07 episodes per person-year.[3]

UTIs are subdivided into cystitis (lower tract or bladder infection) and pyelonephritis (upper tract or kidney infection). Cystitis is characterized by symptoms of dysuria, strangury, frequency, urgency, microscopic haematuria and, less commonly, gross haematuria and suprapubic pain. Vaginal discharge is not consistent with UTI. Symptoms are usually of acute onset.[2] Pyelonephritis is characterized by cystitis symptoms plus fever, flank pain, costovertebral angle tenderness, nausea and/or vomiting.[2]

For males aged 17–79 years, the mean annual UTI incidence is 2.2%, and risk factors include penile-vaginal intercourse, insertive anal intercourse, presence of an indwelling urinary catheter, hospitalization and anatomical abnormalities. For males aged ≥80 years, the mean annual UTI incidence rises to 5.3%, and risk factors include presence of an indwelling urinary catheter, hospitalization and anatomical abnormalities associated with aging or disease (e.g. benign or malignant prostatic hyperplasia).[4]

For women aged 15–39 years, the mean annual UTI incidence is 15.2%, and risk factors include vaginal intercourse, delayed postcoital micturition and use of unlubricated condoms. Also, early age at the time of first UTI episode and maternal history of UTI are independent risk factors for recurrent episodes of cystitis. For women aged 40–59 years, the

© 2008 Adis Data Information BV. All rights reserved.

mean annual UTI incidence falls to 11.4% and risk factors broaden to include sexual activities plus the presence of an indwelling urinary catheter, trauma (secondary to intercourse and/or condom use), the presence of urinary tract obstruction (due to diaphragm use, pregnancy) and alterations in vaginal flora (due to spermicide use, antimicrobial use, menstrual cycle, diaphragm use, menopause and pregnancy). Lastly, women aged 60–79 years have a mean annual UTI incidence of 9.7%, and risk factors include sexual activity (controversial finding), presence of an indwelling urinary catheter, hospitalization, trauma (due to intercourse and/or condom use), alterations in vaginal flora (due to menopause, estrogen or hormone replacement therapy, and antimicrobial use), anatomical changes associated with aging (e.g. cystocoele, prolapse, etc.), insulin-dependent type 1 or 2 diabetes mellitus and lifetime number of UTIs.[3,5]

Acute uncomplicated pyelonephritis is much less common than cystitis, with an incidence of 59 episodes/10 000 women/year.[6] This disorder appears to increase in frequency after 15 years of age and to have a predilection for the summer months. Risk factors are similar to those for cystitis.[3]

Only one study exists describing the epidemiology of UTIs in a non-selected population-at-large.[7] In this study, laboratory surveillance was conducted for all community-acquired UTIs among residents of the Calgary Health Region (population 1.2 million) in Canada during 2004 and 2005. Only data from the first isolate per patient were included in the analysis. A total of 40 618 episodes of UTI occurred among 30 851 residents (overall annual incidence was 17.5/1000): 74% of cultures were submitted from ambulatory patients, 18% from hospitalized patients within the first 2 days of hospitalization, and 9% from nursing home residents. The incidence was significantly higher in females than in males (30.0 vs 5.0/1000, respectively; relative risk [RR] 5.98; 95% CI 5.81, 6.15; $p < 0.0001$). After the first year of life, UTI was rare in males until late middle age, at which point a significant increase occurred with each subsequent decade of life. In females, a peak in incidence occurred in the 20- to 29-year-old age group followed by a decline until late middle age when substantial increases subsequently occurred with advancing age. In the very old (80–89 years old), UTI was common (males 638, females 926; overall 851/1000/year). The most frequent pathogens were *Escherichia coli* (70.2%), *Klebsiella pneumoniae* (6.8%) and enterococci (6.3%), with all other organisms represented in <3% of isolates.[7]

The most important risk factors for acute cystitis include history of previous episodes and frequent/recent intercourse. The relative risk of acute cystitis rises 60-fold during a 48-hour period post coitus. The use of spermicides increases the risk of UTI due to *E. coli* and *Staphylococcus saprophyticus* by 2- to 3-fold, regardless of condom and/or diaphragm use.[2]

This paper reviews the diagnosis and treatment of uncomplicated UTI (uUTI), defined as episodes of cystitis or pyelonephritis in healthy, non-pregnant adult women, including postmenopausal women, with no functional or anatomical abnormalities.[3,8] Thus, infections associated with any of the following risk factors known to increase infection risk or treatment failure are excluded from the following discussion: hospital site of acquisition, pregnancy, presence of an indwelling urinary catheter, recurrent urinary tract instrumentation/interventions, symptoms for >7 days upon presentation to the clinician, diabetes and immunosuppression (primary or secondary, due to disease or drug therapy).[9] Although this definition has been extended to young healthy adult men by some investigators, this is controversial and, for the purposes of this article, such UTIs will be considered to be complicated UTIs and excluded.

The literature search utilized the MEDLINE/PubMed and EMBASE search engines using the keywords 'urinary tract infection', 'cystitis', 'pyelonephritis', 'diagnosis' and 'treatment' to locate English language articles from 1950 up to and including January 2008. In addition, further articles were obtained from the bibliographies of articles identified by the electronic search strategy.

1. Natural Course of Uncomplicated Urinary Tract Infection (UTI)

A multicentre, randomized, double-blind, placebo-controlled trial conducted in 18 primary care clinics in Sweden provides a rare view of the natural

© 2008 Adis Data Information BV. All rights reserved.

course of uUTIs in adult women. In this trial, 288 women were randomized to placebo, with 11 withdrawing before visit 1 (on days 8–10) and 111 withdrawing before visit 2 (at 5–7 weeks). Persisting symptoms was the primary reason given for those who left the study before visit 2. Of the 166 placebo recipients completing the trial, 45% had negative cultures at visit 1 and 57% had negative cultures at visit 2. The association between individual symptoms and bacteriuria or bacterial counts was unpredictable, with bacterial genus/species and counts varying considerably over the study period. The spontaneous clinical cure rates were 28% (after 1 week) and 54% (after 5–7 weeks). Taking into account the high withdrawal rate after visit 1, the spontaneous cure rate at study end was 24%. By day 7, approximately 75% of subjects were free from suprapubic and low back pain (90% at visit 2), 45% were free from dysuria and urgency (70% at visit 2), and 30% were free from all symptoms (55% at visit 2). *E. coli* and staphylococci were associated with slower eradication of symptoms than other organisms.[10]

2. Pathophysiology

The majority of uUTIs are caused by Gram-negative aerobes, with *E. coli* isolated in 70–95% of individuals, *Proteus mirabilis* and *Klebsiella* spp. in 1–2% each, and *Citrobacter* spp, *Enterobacter* spp. pseudomonads and others in <1% each. The most commonly isolated Gram-positive aerobes are coagulase-negative staphylococci (*S. saprophyticus*) found in 5–10%, with enterococci isolated in 1–2%, and Group B streptococci, *S. aureus* and others in <1% each. Of note, 5–10% of samples are culture negative.[8]

Age appears to influence the causative pathogens, in that *E. coli* is somewhat less frequently noted in older (>50 years old) compared with younger (15–50 years old) women, while *Klebsiella*, *Enterococcus* and *Proteus* spp. and pseudomonads are noted more frequently in older women.[3] In contrast, *S. saprophyticus* is more commonly noted in younger women.[3]

The mechanism of infection involves pathogens ascending the urinary tract in the vast majority of cases. Uropathogens from the faecal flora colonize the vagina and periurethral area. From here, they ascend to the bladder, a mechanical activity facilitated by vaginal intercourse.[3] The major defensive mechanism protecting women from UTI acquisition is vaginal colonization with lactobacilli. The inverse association of hydrogen peroxide-producing lactobacilli and vaginal *E. coli* counts is well known. At least a portion of the negative effect of spermicide on UTI risk is thought to be due to its suppression of lactobacilli colonization.[3]

The severity of UTI symptoms is largely determined by the virulence of the infecting strain. For example, acute pyelonephritis (the most severe form of UTI) is frequently due to uropathogenic *E. coli* (UPEC). Pathogenicity is a result of a high degree of tissue attachment. Attachment is the mechanism initiating tissue attack by the bacterium as well as the trigger of the innate immune response by the host, leading to inflammation and symptoms.[11]

Attachment is mediated by bacterial surface fimbriae that bind to specific receptors in the host mucosa and trigger the immune response through co-receptors including the Toll-like receptors. Both P-fimbriae and type 1 fimbriae are approximately 1 μm long and 6–7 nm in diameter, composed of over 1000 subunits of similar size and comparable higher order structure, in a right-handed helical arrangement with 3.28 and 3.36 subunits per turn, respectively. At the end of the helix-like rods, a short thin thread (tip fibrillum) is expressed, at which adhesin promotes adhesion to receptors expressed by host cells.[12] P-fimbriae (class II) enhance bacterial persistence and inflammation in the human urinary tract. The P-fimbrial adhesin *pap G* is important in initial colonization of the uroepithelium and activation of cytokine production by uroepithelial cells. Although type 1 fimbriae have been implicated as virulence factors in animal models of UTI, recent data suggest that these fimbriae are poor adhesion enhancers and do not promote inflammation in humans.[13] Other virulence factors include S/F 1C fimbriae, haemolysin, cytotoxic necrotizing factor 1 and the autotransporter subgroup of proteins (e.g. antigen 43).[14] Urinary tract defences include anti-adhesion proteins (Tamm-Horsfall, lactoferrin, lipocalin), antibacterial peptides secreted by uroepithelial cells (α- and β-defensins, cathelicidin) and chemokine-induced attraction of inflammatory cells.[15] Inflammatory cell recruitment

© 2008 Adis Data Information BV. All rights reserved.

and elimination of uropathogens are controlled by chemokine receptor expression.[11]

3. Diagnosis

A study conducted in nine general practices in southern Wales sought to determine how well physicians can target antimicrobial therapy to adult women with microbiologically confirmed UTI and avoid therapy in those who have negative urine cultures. The association between antimicrobial prescribing and urine culture results was assessed in a population of symptomatic patients with clinically suspected uUTI. Of 113 women (median 54 years old), 61% received empirical therapy. There was a very low degree of agreement between the decision to prescribe empirical therapy and the subsequent culture result ($\kappa = 0.04$): 60% of those prescribed empirical therapy had negative culture results and 25% of those with positive culture results were not prescribed empirical therapy. Thus, clinicians cannot distinguish between patients with or without significant bacteriuria in the context of routine medical care.[16]

The performance characteristics of diagnostic tests were evaluated in an open study of 1993 Dutch women (43 ± 17 years old; range 11–70 years) with complaints consistent with uUTI. For the nitrite test, the positive predictive value, negative predictive value, specificity and sensitivity were 96%, 30%, 94% and 44%, respectively. A negative nitrite result together with a positive leukocyte esterase result had a high positive predictive value (79%) and sensitivity (82%). In this trial, 94% of patients with a positive nitrite test result, 71% of those with negative nitrite plus positive leukocyte esterase results, and 20% of those with negative nitrite and leukocyte esterase results were treated (primarily with nitrofurantoin or trimethoprim).[17]

A study was conducted in 231 women aged 20–92 years (mean age 44 years) presenting to family practitioners with symptoms suggestive of cystitis. All women underwent a standardized clinical assessment, and provided urine for dipstick testing and culture purposes. Urine cultures were positive in 123 subjects (53.3%). Antimicrobials were prescribed to 186 women (81%; 74 of these or 40% were culture negative). Unnecessary antimicrobial therapy would have been reduced by requiring urine dipstick test results positive for pyuria, but some women would have had treatment delayed pending urine culture results. Mandating positive results of testing for pyuria and nitrites would also have reduced unnecessary antimicrobial use as well as minimized the number of subjects with delayed therapy initiation pending urine culture results. Authors derived the following algorithm: considering four characteristics (i.e. urinary symptoms for at least 1 day, dysuria, positive leukocyte esterase and positive nitrites), a urine culture should be obtained where fewer than two of these characteristics are present, but empirical treatment without obtaining a pre-therapy urine culture is acceptable if two or more of these characteristics are present.[18]

In a pooled analysis of nine trials, the diagnostic accuracy of signs and symptoms (obtained via medical history and physical examination) in uUTI was assessed. The presence of four symptoms and one sign significantly increased the probability of UTI: summary positive likelihood ratios for dysuria, frequency, haematuria, back pain and costovertebral angle tenderness were 1.5, 1.8, 2.0, 1.6 and 1.7, respectively. In contrast, the following five findings significantly decreased the probability of UTI: summary negative likelihood ratios for absence of dysuria, absence of back pain, history of vaginal discharge, history of vaginal irritation and vaginal discharge on examination were 0.5, 0.8, 0.3, 0.2 and 0.7, respectively. The two most robust findings were history of vaginal discharge and history of vaginal irritation. Combining symptoms resulted in more robust likelihood ratio results. For example, a combination of dysuria plus frequency without a history of vaginal discharge or irritation raised the probability of UTI to >90%, ruling in the UTI diagnosis on the basis of medical history alone. A urine culture appears to be best utilized when patients present with a suspicion of UTI, but a mostly negative medical history and physical examination.[19]

Urine cultures are also recommended if pyelonephritis or a complicated UTI is suspected. Urine cultures should be obtained for recurrent cystitis, cystitis unresponsive to recommended empirical therapy and, perhaps, in those who are diabetic or immunocompromised as a result of disease(s) and/or drug therapy.[2,3] Bacterial counts as low as

© 2008 Adis Data Information BV. All rights reserved.

10^2 colony-forming units (cfu)/mL are significant if the patient is symptomatic.[3]

Authors from the UK evaluated a new algorithm for the diagnosis of uUTI and its effect on trimethoprim resistance in *E. coli*. The presence of high versus low risk clinical criteria in conjunction with the results of nitrite and leukocyte esterase urine testing were used to guide the need for empirical therapy and use of urine culture. Trimethoprim was the empirical antimicrobial selected for first-line therapy. A high clinical risk together with a positive urine test (to one or both analytes) supported the diagnosis, suggesting that urine for culture should not be obtained in the community setting (exception: males, children, recurrent disease, pregnancy) and should be obtained in the hospital setting. A high clinical risk together with a negative urine test suggests the potential for an alternative diagnosis. A urine culture should be obtained in both settings. A low clinical risk together with a positive urine test (to one or both analytes) suggests that a UTI is present and that urine cultures should be obtained in both settings. Lastly, a low clinical risk together with a negative urine test excludes UTI and supports not obtaining a urine culture in either setting. Use of this algorithm reduced the number of urine samples obtained in the community setting by 14.2% ($p < 0.0001$) and in the hospital setting by 21.7% ($p < 0.0001$). The more selective use of laboratory testing based on use of the algorithm reduced the procurement of urine cultures. The surprising increase in resistance in *E. coli* (to 6.9% for ampicillin, 1.5% for ciprofloxacin and 34.4% for trimethoprim) can be explained by the more selective use of urine cultures in patients more likely to have been previously exposed to the agents, especially trimethoprim. It was not due to increased antimicrobial use (actually, trimethoprim use fell from 164 g/1000 patients/year to 116 g/1000 patients/year).[20]

4. Antimicrobial Resistance

In vitro antimicrobial resistance data in uUTIs can be found in the supplementary material ['ArticlePlus'] at http://drugs.adisonline.com. Countries represented include the US, Canada, Brazil, New Zealand, France, Germany, Italy, Poland, Czechoslovakia, Spain, Sweden, Turkey, Israel, Central African Republic, Madagascar, Mauritius, Senegal, Sudan, India and the 17 countries participating in the ECO-SENS surveillance trial.[1,7,21-49]

A reasonable quantity of study data exist examining antimicrobial resistance in the clinical setting of the diagnosis and management of uUTIs. One study evaluated the relationship between fluoroquinolone utilization and *E. coli* resistance rates in UTIs in the Olomous region of the Czech Republic. Inpatient utilization data were expressed as defined daily doses per 100 bed-days (DBD), while outpatient utilization data were expressed as defined daily doses per 1000 clients per day (DID). Organisms (*E. coli*) were cultured from the urine of all subjects diagnosed with UTI. A significant increase in fluoroquinolone use in inpatients was seen between 1997 and 2002 (2.52–4.29 DBD; $p < 0.01$). A similar finding was noted in outpatients (0.14 DID in 1997 to 0.95 DID in 2002; $p < 0.01$). From 16 784 urine samples obtained over this period, 9192 *E. coli* isolates were collected. Fluoroquinolone resistance rates increased in *E. coli* isolates from both inpatients (2–9%) and outpatients (1–10%; both $p < 0.01$) over this period. The development of fluoroquinolone-resistant *E. coli* correlated with inpatient utilization ($r = 0.944$; $p = 0.005$) and outpatient utilization ($r = 0.859$; $p = 0.029$).[50]

A retrospective cohort study of women aged 18–65 years with acute uncomplicated cystitis treated at a university health centre and primary care clinics in southeastern Michigan, USA, was conducted from September 1992 to April 1999. Among the 601 study isolates, cotrimoxazole (trimethoprim/sulfamethoxazole) resistance rates rose from 8.1% to 15.8% ($p = 0.01$) and nitrofurantoin resistance rates rose from 0% to 2.9% ($p = 0.03$). Age appeared to exert no significant effect on resistance, since the rates in 18- to 39-year-olds and 40- to 65-year-olds for cotrimoxazole were 11% and 10%, respectively. The current or past use of oral contraceptives exerted no effect either ($p = 0.37$ and $p = 0.86$, respectively). Similar findings were noted regarding hormone replacement therapy use. A history of recurrent UTIs (at least three in the previous year) was also not a significant predictor of the development of resistance. By multiple logistic regression, recent (within 2 weeks) receipt of cotrimoxazole (odds ratio [OR] 16.74; 95% CI 2.90, 96.95; $p = 0.002$)

© 2008 Adis Data Information BV. All rights reserved.

and recent receipt of antimicrobials other than cotrimoxazole (OR 2.37; 95% CI 1.14, 4.95; p = 0.02) were predictors of the development of resistance. Treated empirically with cotrimoxazole, 33 and 71 patients had UTI pathogens that were cotrimoxazole-resistant and cotrimoxazole-sensitive, respectively; the corresponding clinical failure rates were 45.5% and 4.2%. Thus, the presence of a cotrimoxazole-resistant pathogen increased the likelihood of clinical failure during cotrimoxazole therapy by approximately 10-fold (RR 10.76; 95% CI 3.34, 34.62; p < 0.0001). Adjusting for confounders raised this value to approximately 17-fold (OR 17.45; 95% CI 4.44, 68.57; p < 0.0001). The mean durations of therapy in clinical failures and clinical successes were 3.4 and 4.9 days, respectively (p = 0.0037).[51]

A similarly designed retrospective study was conducted in the emergency room of a tertiary care university hospital in Tennessee, USA. The study population comprised 448 patients who were at least 14 years old with a UTI due to coliform bacteria; 15% of isolates were cotrimoxazole resistant. By univariate analysis, patients with trimethoprim-resistant pathogens were older (41.7 vs 34.5 years; p < 0.005), more likely to be aged over 65 years (19.4% vs 10.8%; p = 0.04), to have a urinary catheter in place (17.9% vs 6.6%; p = 0.002), to have diabetes (13.4% vs 5.0%; p = 0.008), be neurologically abnormal (19.4% vs 7.1%; p < 0.001), have been hospitalized recently (17.9% vs 8.4%; p = 0.016), be currently receiving at least one antimicrobial (43.3% vs 6.8%; p < 0.001) and to have been recently or currently receiving cotrimoxazole (43.3% vs 6%; p < 0.001) compared with those harbouring trimethoprim-sensitive pathogens. Upon multiple logistic regression analysis, only the following four independent predictors for trimethoprim resistance were found: (i) presence of diabetes (OR 3.1; 95% CI 1.2, 8.4); (ii) recent hospitalization (OR 2.5; 95% CI 1.1, 5.7); (iii) current recipient of one or more antimicrobials (OR 4.5; 95% CI 2.0, 10.2); and (iv) current or recent recipient of cotrimoxazole (OR 5.1; 95% CI 2.2, 11.5).[52]

In a prospective study conducted between October 2000 and October 2003 in the UK, 497 women (aged 18–70 years) with two or more symptoms of acute uUTI (for ≤7 days) were enrolled. Resistance to trimethoprim was noted in 13.9% of isolates. All were treated with trimethoprim 200 mg twice daily for 3 days. Comparing the results in patients with trimethoprim-resistant isolates versus those in patients with trimethoprim-sensitive isolates, those with resistant isolates had a longer median time to symptom resolution (7 vs 4 days; p = 0.0002), a greater proportion required reconsultation to the clinic (39% vs 6% in the initial week; p < 0.0001), a greater proportion needed subsequent antimicrobial therapy (36% vs 4% in the initial week; p < 0.0001) and a greater proportion had significant bacteriuria at the 1-month follow-up (42% vs 20%; p = 0.04).[53]

In yet another case-control study of the effect of previous antimicrobial therapy on the risk of UTI due to resistant *E. coli*, ten general practices in the UK enrolled 903 patients. In this trial, outcomes were assessed prospectively. Case patients were those with ampicillin- or trimethoprim-resistant isolates, while control patients were those with susceptible isolates. Risk of ampicillin resistance was associated with amoxicillin use for ≥7 days in the previous month (OR 3.91; 95% CI 1.64, 9.34) and previous 2–3 months (OR 2.29; 95% CI 1.12, 4.70) before index UTI onset. Use for <7 days was not associated with an increased resistance risk. There was also a significant trend (p < 0.0001) in ORs for length of time between the most recent amoxicillin use and the risk of resistance (i.e. the closer the time of use to the index UTI, the greater the resistance risk – concurrent use OR was 9.34; 95% CI 1.12, 78.01). There was also a significant association between the number of uses in the previous 12 months and the risk of resistance (ORs were 1.44, 2.28 and 5.71 for one, two and three or more uses, respectively; p < 0.0001). Higher amoxicillin doses (500 mg) were not significantly associated with resistance risk, while lower doses (250 mg) were associated with resistance (OR 2.07; 95% CI 1.39, 3.06).[54]

Risk of trimethoprim resistance was associated with trimethoprim use for ≥7 days in the previous month (OR 8.44; 95% CI 3.12, 22.86) and the previous 2–3 months (OR 13.91; 95% CI 3.32, 58.31) before index UTI onset. For trimethoprim use for <7 days, only use in the previous month was significantly associated with resistance risk (OR 4.03; 95% CI 1.69, 9.59). As with ampicillin, there was also a significant trend (p < 0.0001) in ORs for length of time between the most recent trimethoprim use and

© 2008 Adis Data Information BV. All rights reserved.

the risk of resistance (concurrent use OR was 4.93; 95% CI 2.61, 9.30). Again, as with ampicillin, there was a significant association between the number of uses in the previous 12 months and the risk of resistance (ORs were 2.08, 2.05 and 7.53 for one, two and three or more uses, respectively; $p < 0.0001$). The effect of dosage could not be investigated. This study found that within the community setting, previous antimicrobial exposure was a strong risk factor for the emergence of drug-resistant *E. coli*. High-dose, short duration therapy may reduce the effect of this selection pressure.[54]

A recent article has evaluated the results of three cystitis trials from the perspective of outcome of uUTI due to antimicrobial-sensitive and -resistant uropathogens. In study one, 135 patients were randomized to receive cotrimoxazole: 14 had a UTI due to a cotrimoxazole-resistant uropathogen, while 121 had a UTI due to a sensitive uropathogen. Corresponding day 14 bacteriological eradication rates were 50% and 86%. Ten women with UTIs due to cotrimoxazole-resistant uropathogens (study two) had clinical cure and bacteriological eradication rates of cotrimoxazole therapy of 60% and 50%, respectively. In study three, the cotrimoxazole resistance rate among uropathogens in the study population was 29%. On day 7 of cotrimoxazole therapy, clinical cure rates in those with cotrimoxazole-resistant and -sensitive uropathogens were 54% and 88%, respectively, while corresponding bacteriological eradication rates were 42% and 86% ($p < 0.001$). Similar results were found at late study follow-up. Overall, if the uropathogen is resistant to cotrimoxazole, one can expect cotrimoxazole therapy to result in clinical failure rates of 40–50% and bacteriological failure rates of up to 60%. In fact, a modelling analysis produced the following results: assuming a 10% prevalence of cotrimoxazole resistance among uropathogens, the expected clinical cure and bacteriological eradication rates would be 92% and 89%, respectively; assuming a 20% prevalence of cotrimoxazole resistance, corresponding values would be 88% and 84%.[55]

A retrospective case-control study was conducted at a US Veterans Affairs Medical Center using data generated from July 1996 to December 1999, evaluating the risk factors for cotrimoxazole-resistant Gram-negative uropathogens. In the 393 subjects with evaluable data, 53% were aged ≥65 years at the time of their UTIs and 32%, 25%, 6%, 4%, 33% had been seen in primary care, emergency room, women's health, urology, other outpatient specialty clinics, respectively. The overall cotrimoxazole resistance rate was 13%, with no significant fluctuation from year to year. Prior antimicrobial use was prevalent in this study population: 40%, 32% and 23% for cotrimoxazole, fluoroquinolones and penicillins, respectively. Antimicrobial exposure within 6 months was strongly associated with the probability of isolation of a cotrimoxazole-resistant uropathogen (OR 4.4). Exposure to any antimicrobial was seen in 61% of subjects with cotrimoxazole-resistant organisms compared with 27% of those with cotrimoxazole-sensitive organisms ($p < 0.0001$). Corresponding percentage exposures to fluoroquinolones, cotrimoxazole and tetracyclines were 22% vs 8% (OR = 3.0; $p = 0.004$), 27% vs 11% (OR = 2.9; $p = 0.003$) and 10% vs 1% (OR = 19.6; $p < 0.001$), respectively. This relationship appeared to be 'dose dependent' as well, with an increasing probability of cotrimoxazole resistance as the number of exposures and/or number of antimicrobials increased. For example, the resistance rate rose from 8% with one exposure to 39% with three or more exposures ($p = 0.01$ for trend).[56]

All postmenopausal women enrolled in an Israeli managed care organization (Leumit Health Fund) were evaluated for the presence of uUTIs due to *E. coli* between January and May 2005. This population was then stratified into 5-year age strata and strata-specific ofloxacin resistance rates versus *E. coli* were calculated. Among 1291 isolates, the overall crude resistance rate was 8.7%. Those for the age strata of 41–45, 46–50, 51–55, 56–60, 61–65, 66–70 and 71–75 years were 3.2%, 5.6% (OR 2.1), 7.1% (OR 2.4), 9.7% (OR 3.6), 7.8% (OR 2.8), 14.2% (OR 5.3) and 19.9% (OR 8.1), respectively ($p < 0.001$ for linear trend). For the age stratum of 56–75 years, the rate was 19.9%. These results suggest that, in this managed care postmenopausal (aged >55 years) female subpopulation, fluoroquinolones should not be used as empirical therapy.[57]

Canadian investigators have studied the distribution of cotrimoxazole resistance genes and the role of horizontal gene transfer and clonal expansion in recent rises in antimicrobial resistance rates among

© 2008 Adis Data Information BV. All rights reserved.

uropathogenic *E. coli* in Europe and Canada. The authors evaluated 217 such strains. Horizontal gene transfer (via integrons, plasmids or transposons) are now thought to play a larger role than clonal expansion in the increase in cotrimoxazole resistance rates in Europe and Canada.[58] Horizontal gene transfer broadly disseminates resistance genes across wide geographical areas, resulting in many differing resistance gene combinations in a given organism. In this case, regionally independent gene distributions would be expected. In the case of clonal expansion, region-dependent gene distributions would be expected (i.e. each region has individual strain[s] with unique resistance gene combinations). The relative contributions of horizontal gene transfer and clonal expansion to the spread of antimicrobial resistance varies greatly by organism and by type of resistance determinant.

A retrospective cohort review study assessed whether the risk factors for multidrug resistance could also identify cotrimoxazole resistance. These risk factors included age ≥65 years, presence of an indwelling bladder catheter, antimicrobial exposure or hospitalization within the previous 3 months, being postmenopausal, and residence in a long-term care facility.[59] All women presenting to the emergency room between February 2004 and January 2005 with a diagnosis of uUTI formed the study population. In these 215 women, 94 (44%) were 'at-risk' for multiresistant pathogens as defined here and 121 (56%) were not. Median age was 36 years and 75% of isolates were *E. coli*. The overall cotrimoxazole resistance rate was 24%. Cotrimoxazole resistance occurred in 31% of isolates from the 'at risk' population and 18% of the remaining isolates ($p = 0.02$). Thus, risk factors for multidrug resistance also appear to increase the risk for isolated cotrimoxazole resistance in uropathogens associated with uUTIs.[60]

Using data from 311 nonhospitalized patients with community-acquired UTIs due to *E. coli* or *K. pneumoniae* over a 2-year period, Israeli investigators determined the risk factors for isolates being producers of extended-spectrum β-lactamases (ESBL). Independent risk factors by multivariate logistic regression included hospitalization within the previous 3 months (OR 8.95), receipt of antimicrobials within the previous 3 months (OR 3.23), age >60 years (OR 2.65), diabetes (OR 2.57), male gender (OR 2.47), *K. pneumoniae* infection (OR 2.31), previous use of third-generation cephalosporins (OR 15.8), previous use of second-generation cephalosporins (OR 10.1), previous use of fluoroquinolones (OR 4.1) and previous use of penicillin (OR 4.0). All risk factors taken together produced a positive predictive value of 66.4% and negative predictive value of 89.6%.[61]

The virulence characteristics and resistance patterns of ESBL-producing and non-producing *E. coli* isolated from the urine of Croatian patients with uUTIs were compared. These isolates from the Zagreb region were collected over a 5-month period. A total of 39 (1.6%) ESBL-producing strains were identified from a total of 2451 *E. coli* strains. The control group of 45 ESBL-non-producing strains were selected at random from the remaining 2412 isolates. Serogroup 04, haemolysin production, expression of P- and type 1 fimbriae, and resistance to aminoglycosides were significantly more prevalent in the ESBL-producing strains ($p < 0.01$). The prevalence of cotrimoxazole resistance did not significantly differ between the groups. Chromosomal DNA analysis by pulsed-field gel electrophoresis revealed a substantial genomic similarity among the ESBL-producing strains; hence, exhibition of clonal propagation.[62]

The PHARMO medical record linkage system was used to evaluate treatment failures in uUTIs in 320 000 community-dwelling inhabitants of eight medium-sized cities in the Netherlands (from January 1992 to December 1997). During this period, 16 703 women received index courses of trimethoprim, nitrofurantoin or norfloxacin. Treatment failure was defined as the need for further treatment with one of these agents or for cotrimoxazole, amoxicillin, ciprofloxacin or ofloxacin within 31 days after the end of the index course. Failure rates for trimethoprim, nitrofurantoin and norfloxacin were 14.4%, 14.4% and 9.6%, respectively (also, 3-day nitrofurantoin therapy = 18.9%, 3-day trimethoprim therapy = 15.6%). Failure rates were affected by the age of the patient (45–54 and 55–64 years increased risk by 19% and 26%, respectively), year of treatment (start during 1994–6 and 1997–8 increased risk by 17% and 22%, respectively) and prior hospitalization (within past year increased risk by 31%). By

© 2008 Adis Data Information BV. All rights reserved.

multivariate logistic regression analysis, 5 and 7 days of trimethoprim and nitrofurantoin therapy were significantly more effective than 3 days of therapy. In addition, 3, 4 or 5 days of trimethoprim and 5 or 7 days of norfloxacin therapy were significantly more effective than 3 days of nitrofurantoin therapy (by 18–29% and 40–58%, respectively).[63]

A nested case-control study with prospective outcome measurement was utilized to evaluate the clinical outcomes of UTI treatment in a primary care setting (ten general practices in Wales). Patients with symptoms consistent with acute uUTI and laboratory-confirmed *E. coli* infection were followed-up until 1 month after the completion of all UTI-related visits. Of 932 enrollees, 420 patients had *E. coli* isolates resistant to at least one of the four study antimicrobials (ampicillin, trimethoprim, amoxicillin/clavulanic acid and a cephalosporin). In an adjusted multivariate logistic regression analysis, patients were at 2.9-fold increased risk for 'feeling poorly', 3.4-fold increased risk for pain/frequency and 3.4-fold increased risk for 'being out of action', all for >5 days versus 0–5 days, when their isolates were resistant to at least one study antimicrobial and resistant to the antimicrobial prescribed. Similar results were noted for isolates resistant to ampicillin and to the antimicrobial prescribed as well as to trimethoprim and to the antimicrobial prescribed. If a patient had an isolate resistant to at least one study antimicrobial and resistant to the antimicrobial prescribed, (s)he would have a 60% increase in the number of days with any one symptom compared with patients having isolates sensitive to all study antimicrobials ($p = 0.001$). If the patient had an isolate resistant to ampicillin and resistant to the antimicrobial prescribed, the increase in days was 72% ($p < 0.001$). If the patient had an isolate resistant to trimethoprim and resistant to the antimicrobial prescribed, the increase in days was 56% ($p < 0.001$). In contrast, if the isolate was sensitive to the prescribed antimicrobial, only co-resistance to trimethoprim could lead to a significant increase (70%) in the number of days with any one symptom compared with those having isolates sensitive to all antimicrobials ($p < 0.001$). The median maximum reported numbers of days with at least one symptom was 5 days (isolates sensitive to all antimicrobials), 12 days (isolates resistant to trimethoprim; $p < 0.001$), 7 days (isolates resistant to ampicillin; $p = 0.029$) and 7 days (isolates resistant to any antimicrobial; p-value not significant). Resistant isolates also increased physician workload. There were significant increases in the risks of revisiting the physician within 30 days of the index UTI for a 'new' UTI: 1.47-fold for those infected with isolates resistant to at least one antimicrobial, 1.49-fold for those infected with ampicillin-resistant isolates and 2.48-fold for those infected with trimethoprim-resistant isolates (all $p < 0.05$). There were parallel increased risks of needing to change the prescribed agent (2.3-, 2.2- and 7.1-fold; all $p < 0.05$).[64]

A large study of 15- to 44-year-old women with diagnoses of UTI or cystitis was conducted using the UK General Practice Research Database (1992–9). Fourteen percent of 75 045 newly diagnosed patients with UTI/cystitis received a second antimicrobial within 28 days (indicating failure of the first antimicrobial course). Those at risk for this second course included older women (aged 35–44 vs 15–24 years), patients who were pregnant and patients with diabetes. This 14% rate remained stable over time. Using trimethoprim as a reference, patients prescribed amoxicillin were significantly more likely to need a second course of antimicrobials. Cotrimoxazole recipients were significantly less likely to need further treatment compared with trimethoprim recipients. In contrast, nitrofurantoin, the fluoroquinolones and the cephalosporins were not significantly different from trimethoprim in terms of need for a second course of antimicrobials. Lastly, 3, 5 and 7 days of trimethoprim therapy were equally effective (p-value not significant).[65]

In summary, cotrimoxazole (trimethoprim) resistance among uropathogens has been steadily increasing over the past 20 years or so, with high resistance rates being observed in Spain, Portugal, Israel (25–29%) and Latin America (50%).[66] Among the fluoroquinolones, resistance rates are also steadily increasing in a worrisome fashion, with higher rates in Spain, Portugal, Latin America and Asia (7–24%).[66] In general, resistance rates have not risen over time with nitrofurantoin, and the drug is still active against cotrimoxazole- and fluoroquinolone-resistant *E. coli*. However, a resistance rate of 80% among *E. coli* isolates in an Indian hospital outpatient clinic (with concurrent resistance rates

© 2008 Adis Data Information BV. All rights reserved.

against cotrimoxazole and fluoroquinolones of 76% and 69%, respectively) is worrisome.[47] In addition, the lesser potency and higher resistance rates of nitrofurantoin against other Enterobacteriaceae, especially *Proteus* spp., must by considered *vis-à-vis* empirical therapy. Many risk factors for the development of resistance have been identified, including antimicrobial selection pressure from environmental exposure, recent receipt of antimicrobials, increasing age, recent hospitalization, and presence of complicating factors such as urethral catheterization and diabetes. Lastly, the clinical and bacteriological consequences of antimicrobial resistance are now well known, with resistant pathogens resulting in poor clinical and bacteriological cure rates and frequent reinfection unless an alternative agent to which the organism is sensitive is substituted.

Positive urinary tract culture results often represent asymptomatic bacteriuria, which virtually never requires antimicrobial therapy. Avoiding treatment of asymptomatic bacteriuria should reduce the risk of development of antimicrobial resistance. The development of a hospital and ambulatory performance measure for not treating asymptomatic bacteriuria has been proposed. This would be a similar approach to that previously initiated by the US Centers for Disease Control and Prevention to discourage antimicrobial therapy of upper respiratory illnesses.[67]

5. Recent Approaches to Diagnosis and Management

The results of recent survey/questionnaire/observational studies of diagnosis and therapy of uUTIs are reviewed in this section. Countries represented include the UK, Italy, US and the Netherlands.[17,68-73]

A questionnaire was sent to a stratified random sample of general practitioners in Wales. Six clinical scenarios were presented. For the 'probable UTI in a female child' and 'probable asymptomatic bacteriuria in pregnancy' scenarios, nearly all practitioners indicated that they would obtain a urine culture. In the 'treatment failure in an older woman' and 'recurrent UTIs in a male diabetic' scenarios, there was some inter-practitioner variation: 90% and 81% indicated that they would obtain a urine culture, respectively. The greatest variability occurred in the 'probable uUTI' and 'early patient symptoms (with patient pressure to prescribe)' scenarios (56% and 33% indicated that they would obtain a urine culture, respectively).[68]

Italian physicians were followed over a 4-year period using the Health Search Database (a general practitioner research database).[69] The total eligible study population was 457 672 subjects aged ≥16 years followed-up until December 2002. Individuals with acute uncomplicated/complicated cystitis and recurrent cystitis were followed-up. From 1999 to 2002, there were 35 129 cases (96% were acute cystitis and 39.2% of these were uncomplicated). The prevalences of acute complicated and uncomplicated cystitis increased slightly over the 4-year period, while the prevalence of recurrent cystitis remained about the same. No diagnostic tests were done in most patients with cystitis. Over 70% of patients were prescribed at least one course of antimicrobials. Over the 4-year period, there was a 4-fold increase in antimicrobial use for acute cystitis. In 2002, the prevalence of antimicrobial use reached 86.2% for both acute uncomplicated and complicated cystitis, and 81.5% for recurrent cystitis. Fluoroquinolones were the most frequently prescribed antimicrobials during this period (pooled 40% usage rate in uncomplicated cystitis) but prevalence did fall dramatically over time. Fosfomycin use rose dramatically (from 2–5% to 26–34%), becoming the drug of choice in all types of cystitis. The acute uncomplicated cystitis group (n = 13223) had a mean age of 35.3 years, and proportions in the 17–45 year and 46–65 year age groups were 84.8% and 15.2%, respectively. No diagnostic tests, urine culture and sensitivity, or urine culture alone were obtained in 74%, 16% and 10% of cases, respectively. Antimicrobials were prescribed to 77% (prevalence of use increased from 59% in 1999 to 86% in 2002).[69]

A survey of practicing physicians was conducted between 1989 and 1998 (US National Ambulatory Medical Care Survey).[70] Eligible subjects were 18- to 75-year-old women diagnosed with a uUTI (n = 1478). Over the decade, visits to primary care physicians for UTI increased (OR 1.61; 95% CI 1.01, 2.57). The frequency of ordering baseline urinalysis tests fell from 90% to 81% (OR 0.54; 95% CI 0.34, 0.85). Approximately two-thirds of visits

© 2008 Adis Data Information BV. All rights reserved.

culminated with prescription of an antimicrobial (no significant change over the decade). Utilization of cotrimoxazole fell from 48% (1989–90) to 24% (1997–8) [adjusted OR 0.32; 95% CI 0.20, 0.51 per decade]. In contrast, recommended fluoroquinolone use (i.e. ciprofloxacin, [lev]ofloxacin, norfloxacin) rose from 19% to 29% (OR 2.12; 95% CI 1.26, 3.56), nitrofurantoin use from 14% to 30% (OR 2.55; 95% CI 1.50, 4.31) and non-recommended antimicrobials from 33% to 46% (OR 1.57; 95% CI 1.00, 2.44). Internists were more likely to prescribe fluoroquinolones, while obstetricians were more likely to prescribe nitrofurantoin. Regarding primary care physicians and cotrimoxazole use, patients aged <45 years were more likely to receive cotrimoxazole (OR 2.1; 95% CI 1.38, 3.20), while those with a history of recurrent UTIs were less likely to receive it (OR 0.37; 95% CI 0.23, 0.59). Obstetricians were less likely to prescribe cotrimoxazole than were general practitioners (OR 0.47; 95% CI 0.22, 0.99). Regarding primary care physicians and fluoroquinolone use, patients aged <45 years (OR 0.64; 95% CI 0.41, 0.99) and non-Whites (OR 0.38; 95% CI 0.19, 0.77) were less likely to receive fluoroquinolones. Obstetricians were less likely to prescribe fluoroquinolones than were primary care physicians (OR 0.47; 95% CI 0.22, 0.99). Regarding primary care physicians and nitrofurantoin use, obstetricians were more likely to prescribe it than were general practitioners (OR 3.19; 95% CI 1.85, 5.53) and its use in managed care organizations rose over the decade (OR 1.92; 95% CI 1.12, 3.29). Non-Whites (OR 1.81; 95% CI 1.10, 2.97) and those with a history of recurrent UTIs (OR 1.82; 95% CI 1.20, 2.75) were more likely to receive non-recommended antimicrobials. Obstetricians were more likely to prescribe them (OR 2.37; 95% CI 1.41, 3.99), while internists were less likely (OR 0.62; 95% CI 0.40, 0.96). In contrast, a short visit led to reduced use of these agents (OR 0.60; 95% CI 0.40, 0.91).[70]

A similar US survey was conducted from 2000 to 2002, but with hospital clinic and emergency room visits also surveyed. The study population comprised 2638 individuals seen in outpatient, hospital clinic and emergency room visits for uUTIs. Urinalysis and urine cultures were performed in 76% and 23%, respectively. Fluoroquinolones, cotrimoxazole and nitrofurantoin were prescribed at 44%, 30% and 18% of visits, respectively (2000–2) and 48%, 33% and 0% of visits, respectively (2002 only, $p < 0.04$). Significant predictors of fluoroquinolone use included advancing age (those aged 30–49 and ≥50 years were more likely than those aged 18–29 years to receive fluoroquinolones [OR 1.52; 95% CI 1.10, 1.96 and OR 1.64; 95% CI 1.15, 2.14, respectively]) and location (patients in the Midwest and West were less likely to receive fluoroquinolones than those in the Northeast [OR 0.73; 95% CI 0.50, 0.97 and OR 0.66; 95% CI 0.41, 0.97, respectively]). Being an obstetrician was a significant negative predictor for prescribing fluoroquinolones (RR 0.31; 95% CI 0.11, 0.73). In 2002, ciprofloxacin (61% of the market) and levofloxacin (32% of the market) were the most frequently prescribed fluoroquinolones.[71]

A survey was conducted in four US states (Nebraska, Alabama, Pennsylvania and Minnesota) among internists, family practitioners, obstetricians/gynaecologists, and emergency medicine practitioners to evaluate approaches to diagnosis and treatment of UTIs. Of 8942 physicians surveyed, 2172 (24.3%) responded. Participants were given the case of a "non-pregnant 30-year-old woman with an uncomplicated UTI characterized by dysuria of recent onset". Most (79%) said that they usually or always obtain a urinalysis but only 30% would obtain a urine culture. Obstetricians/gynaecologists were more likely to order a urine culture (44%), but less likely to order a urinalysis and leukocyte esterase (41%). Emergency room practitioners were more likely to order leukocyte esterase (71%). In terms of tests performed in the office, dipstick urinalysis, microscopic urinalysis and urine cultures were obtained by 93%, 80% and 29%, respectively. The threshold for a 'significant' colony count on urine culture was felt to be $\geq 10^5$ cfu/mL by 55% and 10^2 cfu/mL by just 6%. Most chose either 2–5 days (internists, emergency room practitioners) or 6–10 days (obstetricians/gynaecologists) of therapy. Most chose cotrimoxazole as the antimicrobial-of-choice (77–88%) but obstetricians/gynaecologists chose nitrofurantoin (46%) followed by cotrimoxazole (39%) [overall, 13% chose nitrofurantoin]. If the urine culture came back negative, only 23% would stop antimicrobials. Most would continue them unchanged (47%) or shorten the therapy

© 2008 Adis Data Information BV. All rights reserved.

course (22%). In the case of a "woman with dysuria and a positive urinalysis for pyuria and bacteriuria", 63% would start antimicrobials without further testing, 21% would wait for the urine culture results and 34% would order a urine culture followed by an empirical antimicrobial. In the context of equivocal urinalysis results, 39% would start antimicrobials without further testing, 16% would wait for urine culture results and 39% would order a urine culture followed by an empirical antimicrobial. Lastly, family practitioners and emergency medicine practitioners made greater use of follow-up visits than did other physicians. One might wonder at the causes of these differences between prescribers.[72]

A study conducted in the Netherlands in 1993 assessed antimicrobial utilization and resistance rates in adult women with uUTI. Seventy percent of patients were treated empirically with antimicrobials (nitrofurantoin 57–68%, trimethoprim 18–23%). The nitrofurantoin prescription rate fell and fluoroquinolone prescription rate rose with increasing age. The duration of nitrofurantoin therapy was 3–7 days. Three-day therapy with trimethoprim was used in 80% of 21- to 50-year-olds, while 5-day therapy was used in older patients. Fluoroquinolones were prescribed for 7 days in nearly all recipients. *E. coli* frequency fell with increasing age but the reduction was a very modest 4%. *Proteus mirabilis* was found mostly in older patients (1% vs 4% vs 6% in those aged 11–20, 21–50 and 51–70 years, respectively); as expected, *S. saprophyticus* frequency was increased in younger patients (7% vs 4% vs 0.5%, respectively). The antimicrobial susceptibility of *E. coli* was not related to patient age. Amoxicillin (67%) and trimethoprim (77%) had the lowest levels of susceptibility of tested agents. Fluoroquinolone resistance was beginning to emerge in older patients.[17]

One hundred consecutive emergency department patients in two academic medical centres (Philadelphia, Pennsylvania, USA) who received a fluoroquinolone and were subsequently discharged formed the population of a study of inappropriate antimicrobial use. Eighty-one patients received a fluoroquinolone for an inappropriate indication: in 43 (53%) it was inappropriate because another agent was really the drug of choice; in 27 (33%) there was no evidence of infection based upon chart documentation; and in 11 (14%), evaluators were unable to assess the need for antimicrobial therapy. In 19 patients, the fluoroquinolone was prescribed for the appropriate indication but only one (5.3%) received the correct dose and duration. The vast majority of these patients had uUTIs where the dose was too high (e.g. levofloxacin 500 vs 250 mg) or treatment was for too long (>7 days). Overall, fluoroquinolone use in UTIs (n = 45) was appropriate in 38 patients (84%) and inappropriate in 7 (16%).[73]

6. Management Strategies

Table I illustrates selected clinical trials of antimicrobial treatment of uUTIs.[2,74-98] Trials were selected either because they comprise recent additions to the literature or because they are 'classic' or 'seminal' trials that have had a significant effect on clinical practice/guideline development.

All UTI studies should be evaluated in light of the following recommendations for optimal uUTI study design.[99] These parameters are used by the US FDA to evaluate the adequacy of UTI research data.[99] Quantitative results of urine culture and urinalysis (i.e. pyuria) are the laboratory cornerstones for establishing the diagnosis of true infection and determining the efficacy of a particular antimicrobial regimen. In symptomatic infection, the documentation of pyuria (≥10 white blood cells/mm^3 of unspun urine) constitutes important evidence for UTI, provided that a rigorous technique for defining pyuria is employed. For acute uncomplicated cystitis in women, significant uropathogen counts are $\geq 10^3$ cfu/mL, while in acute uncomplicated pyelonephritis significant counts are $\geq 10^4$ cfu/mL. These criteria refer to urine collected by clean-catch midstream technique. Clinical criteria for cystitis to target during screening include dysuria, urgency, frequency and suprapubic pain with no urinary symptoms in the 4 weeks prior to the index episode. For acute pyelonephritis, targeted clinical criteria include fever, chills, flank pain and costovertebral angle tenderness; other diagnoses should be excluded and the patient should have no history or evidence of urological abnormalities. Endpoints to be evaluated should include microbiological response, clinical response (including response of pyuria), effect of regimen on reinfection rates and adverse events. Comparators should be either agents in

© 2008 Adis Data Information BV. All rights reserved.

Table I. Selected clinical trials of the antimicrobial treatment of uncomplicated urinary tract infections (uUTIs)

Treatment [study design]	Clinical findings	Tolerability findings
Fluoroquinolones		
Iravani et al.[74] *(1995)*		
Study 1:		
A. Cipro 500 mg × 1 dose (n = 107) B. Cipro 250 mg bid × 7 d (n = 103) [R/DB]	At 4–9 d after therapy, clinical CRs were 85% and 94%, improvement rates were 9% and 6% after treatments A and B (p = significant but no p-values provided). Bacteriological eradication rates were 89% and 98% after treatments A and B (p = significant but no p-value provided). Corresponding bacteriological eradication rates at the 4-wk post-therapy FU visit were 92% and 95% (p = NS)	Treatment-emergent AEs were reported in 18% and 12% of treatment A and B recipients. Corresponding drug-related AE rates were 17% and 11%. The most frequent AEs were related to the GI or GU tracts. No statistical test results provided
Study 2:		
A. Cipro 100 mg bid × 3 d (n = 105) B. Cipro 250 mg bid × 3 d (n = 105) C. Cipro 250 mg bid × 7 d (n = 106) [R/DB]	At 4–9 d after therapy, clinical CRs were 89%, 94% and 95%, and improvement rates were 8%, 6% and 3% after treatments A, B and C (p = NS). Bacteriological eradication rates were 92%, 90% and 94% after treatments A, B and C (p = NS). At the 4-wk FU visit, corresponding eradication rates were 95%, 85% and 93% (p = NS)	Treatment-emergent AEs were reported in 30%, 33% and 28%, and drug-related AEs in 23%, 26% and 23% of treatment A, B and C recipients. Most AEs were referable to the GI and GU tracts. No statistical test results provided
Study 3:		
A. Cipro 500 mg od × 3 d (n = 151) B. Cipro 500 mg od × 5 d (n = 151) C. Norflox 400 mg bid × 7 d (n = 142) [R/DB]	At 4–9 d after therapy, clinical CRs were 97% in all treatment groups, while at the 4-wk FU visit they were 94%, 89% and 95% for treatments A, B and C (p = NS). Bacteriological eradication rates were 92%, 90% and 94% at 4–9 d after therapy and 88%, 80% and 90% at 28 d after therapy in treatment groups A, B and C (both p = NS).	Treatment-emergent AEs were reported in 36%, 27% and 31%, and drug-related AEs in 21%, 13% and 17% after treatments A, B and C. Most AEs were referable to the GI and GU tracts. No statistical test results provided
	Summary: minimum effective dosage regimen of Cipro in women with uUTI is 100 mg bid for 3 d	
Vogel et al.[75] *(2004)*		
Cipro 250 mg bid × 3 d (n = 93)	All subjects in trial aged >60 y. Symptom relief:[a] nocturia = 88%; urgency = 73%;[b] frequency = 73%; burning = 100%; suprapubic pain = 100%; bacteriological eradication = 98%; reinfection = 14%[c]; relapse = 15%[c]	On study d 5, the mean ± SD no. of AEs and frequencies of drowsiness, loss of appetite and abdominal pain were significantly greater in the 7-d group vs 3-d group ($p < 0.001$, $p = 0.003$, $p = 0.001$
Cipro 250 mg bid × 7 d (n = 89) [R/DB]	Symptom relief:[a] nocturia = 83%; urgency = 88%;[b] frequency = 77%; burning = 97%; suprapubic pain = 84%; bacteriological eradication = 93%; reinfection = 18%[c]; relapse = 13%[c]	and $p = 0.05$, respectively). On study d 9, the mean ± SD number of AEs and frequencies of drowsiness, loss of appetite and nausea or vomiting were significantly greater in the 7-d group vs 3-d group ($p < 0.001$, $p < 0.001$, $p = 0.001$ and $p = 0.04$, respectively)
Arredondo-Garcia et al.[76] *(2004)*		
Cipro 250 mg bid × 3 d (n = 97)	Clinical resolution in 88.7%;[d] bacteriological cure in 91.8%;[d] therapy success in 83.5%;[d] therapy failure in 14.4%;[d] clinical resolution in 83.5%;[e] bacteriological cure in 83.5%;[e] therapy success in 77.3%;[e] therapy failure in 13.4%[e]	AEs occurred in 4.0%. AEs related to drug (0.7%)

Continued next page

© 2008 Adis Data Information BV. All rights reserved.

Table I. Contd

Treatment [study design]	Clinical findings	Tolerability findings
Cotrim DS bid × 7 d (n = 81)	Clinical resolution in 86.4%;[d] bacteriological cure in 85.2%;[d] therapy success in 81.5%;[d] therapy failure in 17.3%;[d] clinical resolution in 81.5%;[e] bacteriological cure in 81.5%;[e] therapy success in 75.3%;[e] therapy failure in 13.6%[e]	AEs occurred in 8.7%. AEs related to drug (7.3%)
Norflox 400 mg bid × 7 d (n = 107) [R][f]	Clinical resolution in 84.1%;[d] bacteriological cure in 86.9%;[d] therapy success in 78.5%;[d] therapy failure in 15.9%;[d] clinical resolution in 82.2%;[e] bacteriological cure in 81.3%;[e] therapy success in 80.4%;[e] therapy failure in 6.5%[e]	AEs occurred in 3.9%. AEs related to drug (2.6%)
Hooton et al.[77] *(2005)*		
Amox/Clav 500 mg/ 125 mg bid × 3 d (n = 160); Cipro 250 mg bid × 3 d (n = 162) [R/IB]	Clinical cure (absence of persistent/recurrent symptoms) occurred in 77% of Cipro and 58% of Amox/Clav recipients ($p < 0.001$) [results were similar for isolates susceptible and non-susceptible to Amox/Clav]. Bacteriological cure (no uropathogens on FU UC) occurred in 95% of Cipro and 76% of Amox/Clav recipients ($p < 0.001$) [results were similar for isolates susceptible and non-susceptible to Amox/Clav]. Cipro was significantly superior to Amox/Clav when evaluating the proportions of pts without persistent or recurrent UTIs over time ($p \leq 0.004$) [results were similar for isolates susceptible and non-susceptible to Amox/Clav]. Vaginal colonization was significantly greater in the Amox/Clav recipients compared with the Cipro recipients up to and including the wk 8 visit (p range 0.03 to <0.001)	AEs were reported by 27% of Amox/Clav and 19% of Cipro recipients ($p = 0.06$). Differences were noted mainly in the prevalences of GI and GU AEs (diarrhoea in 8% vs 0.6% and vaginal symptoms in 9% vs 3% of Amox/Clav and Cipro recipients, respectively)
Richard et al.[78] *(2002)*		
A. Gati 400 mg × 1 dose (n = 202) B. Gati 200 mg od × 3 d (n = 201) C. Cipro 100 mg bid × 3 d (n = 201) [R/DB]	Clinical cure occurred in 93%, 95% and 93% of treatment A, B and C recipients at 5–9 d after the EOT (p = NS). Sustained clinical cure at the d 29–42 visit occurred in 90%, 88% and 92% of treatment A, B and C recipients (p = NS). Bacteriological eradication at 5–9 d after the EOT occurred in 92%, 96% and 94% of pathogens in treatment A, B and C recipients (p = NS). Reinfection occurred in 3%, 2% and 5% and persistence in 7%, 6% and 3% of treatment A, B and C recipients (p = NS for both reinfection and persistence)	AE rates and types were similar in the 3 groups
Iravani et al.[79] *(1999)*		
A. Cipro 100 mg bid × 3 d (n = 168) B. Cotrim DS bid × 7 d (n = 174) C. Nitro 100 mg bid × 7 d (n = 179) [R/DB]	At 4–10 d after therapy, clinical cure/improvement occurred in 95%/0, 95%/2%, and 93%/0 of treatment A, B and C recipients (all p = NS). Corresponding bacteriological eradication rates were 88%, 93% and 86% (p = NS). At 4–6 wk after therapy, continued clinical cure occurred in 90%, 90% and 89% of treatment A, B and C pts (all p = NS). Continued bacteriological eradication occurred in 91%, 79% and 82% of treatment A, B and C recipients (A vs B and A vs C, both $p < 0.05$). Bacteriological eradication occurred in 82%, 79% and 76% of pathogens after treatments A, B and C (p = NS for all pairwise comparisons). Race and age had no significant effect on the bacteriological efficacy of the 3 treatments	At least one AE occurred in 28%, 38% and 34% of treatment A, B and C recipients (A vs B; $p < 0.05$). At least one drug-related AE occurred in 20%, 26% and 25% of treatment A, B and C recipients (p = NS). Nausea occurred in 3%, 9% and 11% of treatment A, B and C recipients (A vs B and A vs C; both $p \leq 0.05$). Rash occurred in 1%, 4% and 0.4% of treatment A, B and C recipients (B vs C; $p \leq 0.05$). Vaginitis was noted more frequently after treatment B (2%) vs A (0) [$p \leq 0.05$]

Continued next page

© 2008 Adis Data Information BV. All rights reserved.

Table I. Contd

Treatment [study design]	Clinical findings	Tolerability findings
McCarty et al.[80] *(1999)* A. Cipro 100 mg bid × 3 d (n = 229) B. Oflox 200 bid × 3 d (n = 231) C. Cotrim DS bid × 3 d (n = 228) [R/DB]	Clinical cure was noted in 93%, 96% and 95% of treatment A, B and C recipients (p = NS) at the EOT. At the 4–6-wk FU visit, clinical cure was noted in 91%, 89% and 91% of treatment A, B and C recipients (p = NS). Bacteriological eradication was noted, at the EOT, in 94%, 97% and 92.5% and at the 4–6-wk FU visit in 89%, 87% and 84% of treatment A, B and C recipients (all p = NS except p = significant for B vs C at the EOT; p-value not provided). Bacteriological eradication by organism was similar in the 3 groups (no statistical test results provided)	Treatment-emergent AEs occurred in 31%, 39% and 41% of treatment A, B and C recipients (p = 0.03). Corresponding drug-related AE rates were 26%, 34% and 35% (p = 0.03). AEs led to premature study discontinuation in 2 treatment A, 1 treatment B and 9 treatment C recipients (p = 0.02). The frequencies of individual AEs were similar in the 3 groups
Schaeffer and Stuppy[81] *(1999)*		
Self-start therapy: Norflox 400 mg bid × 3 d (n = 34) to cure index UTI. At each acute episode, pt obtained culture (Uricult®)[9] and initiated therapy. Mailed culture to lab. FU at 5–9 d and 4–6 wk post-therapy [O][h]	84 symptomatic episodes but no cultures in 6. Of 78 cultured episodes, 11 were negative and 67 had growth (*Escherichia coli* in 53, *Staphylococcus* spp. in 5, *Proteus* spp. in 2, *Klebsiella* spp. in 2, *E. coli* and *Klebsiella* spp. in 2, *S. marcescens* in 1, *Klebsiella* and *Enterobacter* spp. in 1 and *Klebsiella* and *Proteus* spp. in 1). 6 women FU for a total of 74 mo (mean 12, range 5–21) had no symptomatic episodes. 28 women FU for a total of 355 mo (mean 11, range 2–33) had 84 symptomatic episodes (1 in 9, multiple in 19). 9 women FU for a total of 103 mo had no culture-documented UTIs, while 25 women had 67 confirmed UTIs (1 in 13, multiple in 12). Symptomatic UTI episode rate = 2.8/patient-year (range 0–9). Microbiologically confirmed UTI rate = 2.3/patient-year (range 0–9). Greatest risk of UTI occurred in first 3 mo (≈20%/mo). Of 84 symptomatic episodes, 78 responded clinically (92%) to Norflox. Of 6 episodes not responding clinically, initial cultures were positive, d 5–9 cultures were negative despite symptoms and 4- to 6-wk cultures were negative (no symptoms, either); 3 of 6 had vaginitis (responded to topical therapy). All 67 positive cultures were negative on d 5–7. All 11 culture-negative but symptomatic pts responded to therapy. In 6 pts and 14/67 (21%) of culture-positive UTIs, clearing was followed by a recurrence 4–6 wk later (11 infections with same organism). All re-treated with Norflox and cured. Across all pts, the mean cost of self-start therapy was $US19/mo (mean $US7 for asymptomatic, mean $US22 for recurrences) [1997 costing]	No pt reported AEs
Henry et al.[82] *(2002)*		
Cipro ER 500 mg od × 3 d (n = 199) Cipro 250 mg bid × 3 d (n = 223) [R/DB]	At 4–11 d after the EOT, clinical cure was noted in 95.5% and 92.7% of Cipro ER and Cipro recipients (p = NS). Bacteriological eradication at this time was noted in 94.5% and 93.7% of Cipro ER and Cipro recipients (p = NS). Corresponding clinical cure and bacteriological eradication rates at 25–50 d after the EOT were 89.0% and 86.6% (p = NS) and 85.8% and 81.3% (p = NS). Bacteriological eradication rates for each pathogen were similar in the 2 groups (no statistical test results were provided)	AE rates (treatment-emergent, drug-related and specific drug-related events) were similar in the 2 groups (no statistical test results provided)

Continued next page

© 2008 Adis Data Information BV. All rights reserved.

Table I. Contd

Treatment [study design]	Clinical findings	Tolerability findings
Fourcroy et al.[83] *(2005)* Cipro ER 500 mg od × 3 d (n = 272) Cipro 250 mg bid × 3 d (n = 251) [R/DB]	At 4–11 d after the EOT, clinical cure was noted in 85.7% and 86.1% of Cipro ER and Cipro recipients (p = NS). Bacteriological eradication at this time was noted in 93.4% and 89.6% of Cipro ER and Cipro recipients (p = NS). At 28–42 d after the EOT, corresponding clinical CRs were 75.7% and 78.8%, while bacteriological eradication rates were 82.4% and 83.2% (both p = NS). Bacteriological eradication rates for each pathogen were similar in the 2 groups (no statistical test results provided)	AEs were reported by 12.7% and 14.7% of Cipro ER and Cipro recipients (p = NS). GI and CNS AEs predominated, being noted in 2.9% vs 5.1% and 2.1% vs 2.9% of Cipro ER and Cipro recipients, respectively (both p = NS). However, nausea and diarrhoea occurred significantly less frequently with the ER compared with the standard (IR) formulation (nausea: 0.6% vs 2.2% [p = 0.033] and diarrhoea: 0.2% vs 1.4% [p = 0.037])
Fosfomycin		
Bonfiglio et al.[84] *(2005)*		
Fosfo 3 g × 1 dose (acute UTI, n = 274; recurrent UTI, n = 113) [O]	Pooled results: At 8–10 d after the EOT, 88.9% and 11.1% of pts were clinically cured or improved. Bacteriological eradication was seen in 91.7%. Pathogen-specific eradication rates ranged from 77.7% to 100% except for *P. aeruginosa* (n = 6; 33% eradication) and *Enterobacter aerogenes* (n = 3; 0% eradication)	AEs were observed in 4.9% (diarrhoea in 12, nausea in 5, vomiting in 2)
Lobel[85] *(2003)*		
Study 1:		
Fosfo 3 g × 1 dose (n = 177) TMP 200 mg bid × 5 d (n = 84) [R]	Bacteriological CRs were 83% in both groups on d 7–9 (p-value not provided). No clinical response data provided	No AE data provided
Study 2:		
Fosfo 3 g × 1 dose (n = 58) Ceph 500 mg qid × 5 d (n = 54) [R]	Clinical CRs (d 5 and 30) were 91% and 86% (Fosfo) vs 91% and 78% (Ceph). Corresponding bacteriological CRs were 91% and 81% vs 83% and 68%. All intergroup comparisons were NS.	No AEs were reported by Fosfo recipients, while 3 Ceph recipients reported AEs (vaginal irritation on d 5 in all 3)
Study 3:		
Fosfo 3 g × 1 dose (n = 61) Norflox 400 mg bid × 7 d (n = 50) [R/DB]	Clinical CRs (d 8–9) were 92% (Fosfo) and 96% (Norflox). Bacteriological eradication rates (8–9) were 90% and 80% with Fosfo and Norflox. Corresponding d 42 bacteriological eradication rates were 62% and 65%. No statistical test results provided	Rates of 'probably-related' AEs were 3% (Norflox) and 13% (Fosfo). In the Norflox pts, there was 1 case each of nausea and diarrhoea. In the Fosfo pts, there were 6 cases of diarrhoea, 3 cases of abdominal pain, 2 cases each of nausea and vomiting and 1 case each of loss of appetite, fatigue and dizziness
Study 4:		
Fosfo 3 g × 1 dose (n = 28) Norflox 800 mg × 1 dose (n = 25) [R/DB]	Clinical CRs were 80% (Fosfo) and 84% (Norflox) on d 7 (p = NS). Bacteriological CRs were 75% (Fosfo) and 84% (Norflox) on d 7 (p = NS)	No significant AEs reported

Continued next page

© 2008 Adis Data Information BV. All rights reserved.

Table I. Contd

Treatment [study design]	Clinical findings	Tolerability findings
Study 5: Fosfo 3 g × 1 dose (n = 113) Nitro 50 mg qid × 7 d (n = 114) [R/DB]	Clinical cure/improvement rates (d 42) were 85/3% (Fosfo) and 82/3% (Nitro) [p = NS]. Bacteriological CRs at d 9 (90% for Nitro vs 81% for Fosfo) and d 42 (93% for Fosfo vs 87% for Nitro) were not significantly different	On d 4, AE rates were significantly different (33% for Fosfo vs 12% for Nitro). Most AEs were referable to the GI tract or CNS. On d 9, AE rates were not significantly different (15% for Fosfo vs 8% for Nitro). Severe AEs occurred in 3 Fosfo and 1 Nitro recipient
Gupta et al.[86] *(2005)*		
A. Cipro 250 mg bid × 3 d (n = 25) B. Nitro 100 mg bid × 7 d (n = 17) C. Fosfo 3 g × 1 dose (n = 20) [R]	>90% clinical and bacteriological CRs with all 3 regimens. Prevalence of rectal *E. coli* post-therapy was significantly decreased by treatments 1 and 3 but not treatment 2 (both p < 0.001). 2 Cipro-resistant *E. coli* strains were isolated from 1 treatment A pt about 10 d after the EOT (also resistant to Amp, Nitro, Tetra, Cotrim, Gent). These 2 strains disappeared by the 30-d FU visit	No AEs reported
Stein[87] *(1999)*		
Fosfo 3 g × 1 dose (n = 269) Nitro 100 mg (macrocrystalline) bid × 7 d (n = 252) [R/DB]	At 5–11 d after the initial treatment dose (visit 1), the clinical cure/improvement rates were 82.1/9.1% (Fosfo) and 84.1/10.6% (Nitro) [p = NS]. Corresponding clinical cure/improvement rates at 5–11 d after therapy (visit 2) were 90.4/4.4% and 88.9/2.8%, and at 4–6 wk after therapy (visit 3) were 91.1/2.5% and 91.7/1.7% (both p = NS). Bacteriological CRs were 78.1% vs 86.3% (visit 1; p = 0.02), 86.9% vs 80.9% (visit 2; p = NS) and 96% vs 91.1% (visit 3; p = NS) in Fosfo and Nitro recipients. The difference in bacteriological response at visit 1 may be explained by the use of Nitro over the first 7 d of the study compared with the absence of Fosfo therapy after d 1	AEs considered definitely or probably drug-related occurred in 5.3% of Fosfo and 5.6% of Nitro recipients (p = NS). AEs led to premature study withdrawal in 1.9% of Fosfo and 4.3% of Nitro recipients (p = NS). The majority of AEs were GI in nature and occurred at similar rates in the 2 groups
Minassian et al.[88] *(1998)*		
Fosfo 3 g × 1 dose (n = 177) TMP 200 mg bid × 5 d (n = 84) [R]	On study d 7–9, bacteriological eradication occurred in 83% of pts in each group. On study d 28–30, continued bacteriological eradication occurred in 85% (Fosfo) and 95% (TMP). No statistical test results provided	No AE data provided

Continued next page

© 2008 Adis Data Information BV. All rights reserved.

Table I. Contd

Treatment [study design]	Clinical findings	Tolerability findings
Miscellaneous		
Raz et al.[89] *(2002)* Cotrim DS bid × 5 d. n = 353 with Cotrim-susceptible pathogens and n = 151 with Cotrim-resistant pathogens. Cotrim-resistant pathogens were recovered from 65% of women with recurrent UTIs and 41% of women without a history of UTI recurrences (p = 0.001) [O]	Bacteriological eradication at 5–9 d after the EOT occurred in 82% and 42% of pts with Cotrim- susceptible or -resistant pathogens (p < 0.001). At 28–42 d after the EOT, the corresponding bacteriological eradication rates were 93% and 70% (p < 0.001). Clinical CRs reflected the microbiological results. Clinical cure occurred in 88% and 54% (at 5–9 d post-therapy) and 93% and 70% (at 28–42 d post-therapy) of pts with Cotrim-susceptible or -resistant pathogens (both p < 0.001)	AEs were noted in 25% of pts and led to treatment discontinuation in 10%. GI reactions, urticaria, fever and agranulocytosis constituted 63%, 18%, 17% and 2% of AEs, respectively
Christiaens et al.[90] *(2002)*		
Nitro 100 mg qid × 3 d (n = 40) Placebo × 3 d (n = 38) [R/DB]	On d 3, clinical cure or improvement was noted in 77% of Nitro and 54% of placebo recipients (p = 0.08). On d 7, corresponding clinical response rates were 88% and 51% (p = 0.003). On d 3, bacteriological eradication was noted in 81% of Nitro and 20% of placebo recipients (p < 0.001). On d 7, corresponding bacteriological eradication rates were 74% and 41% (p = 0.05). FU on d 14 demonstrated no significant differences between the groups in clinical response (p = 0.29) and bacteriological response (p = 0.31). Note the delay in symptomatic response despite bacteriological eradication	AEs were reported in 23% of Nitro and 26% of placebo recipients. The types of AEs were similar in the 2 groups (no statistical test results were provided)
Nicolle et al.[91] *(2002)*		
Pivmec 400 mg bid × 3 d (n = 457) Norflox 400 mg bid × 3 d (n = 444) [R/DB]	Clinical cure or improvement occurred in 95% and 96% of Pivmec and Norflox recipients on d 4, while corresponding clinical CRs were 82% and 91% (Pivmec) and 88% and 91% (Norflox) on d 11 ± 2 and 39 ± 5 (only the d 11 ± 2 CRs were significantly different; p = 0.019). Bacteriological CRs were 75% and 91% on d 11 ± 2 (p < 0.001) and 82% and 84% on d 39 ± 5 (p = NS) in the Pivmec and Norflox recipients. Bacteriological outcomes were poorer, regardless of age, with Pivmec compared with Norflox therapy. In subjects ≤50 years old, respective CRs were 77% and 92% and in subjects aged >50 years, 64% and 90% (both p < 0.001). Clinical outcomes were poorer with Pivmec compared with Norflox therapy only in subjects aged >50 years, wherein CRs were 77% (Pivmec) and 88% (Norflox) [p = 0.04]. Examining the effect of age on Pivmec efficacy, the bacteriological CRs were significantly different in the 2 age groups (p = 0.047) while the clinical CRs were not (p = NS)	AEs were reported by 36% and 39% of Pivmec and Norflox recipients (p = NS). Most AEs were referable to the GI tract. 1.5% and 4.3% of Pivmec and Norflox recipients experienced vaginal candidiasis. Only 8.8% and 9.7% of AEs in Pivmec and Norflox recipients were considered to be probably drug related. Premature study termination rates due to AEs were 0.8% (Pivmec) and 2.1% (Norflox). No results of statistical testing were provided

Continued next page

© 2008 Adis Data Information BV. All rights reserved.

Table I. Contd

Treatment [study design]	Clinical findings	Tolerability findings
Hooton et al.[92] *(1995)* A. Cotrim DS bid (n = 39) B. Nitro[i] 100 mg qid (n = 36) C. Cefadrox 500 mg bid (n = 32) D. Amox 500 mg tid (n = 42) All regimens were 3 d in duration [R]	CRs 6 wk post-therapy were 82% (A), 61% (B), 66% (C) and 67% (D) [A vs B; p = 0.04]. Failure rates (where failure = persistence of initial pathogen at study d 4–6) were 2.5% (A), 16% (B), 0 (C), 14% (D) [A vs B; p = 0.05]. *E. coli* was involved in 12/13 (92%) treatment failures. Early or late UTI recurrences were common in all groups: 3 early and 3 late recurrences (5 *E. coli*, 1 *Klebsiella* sp.; treatment A), 2 early and 6 late recurrences (all *E. coli*; treatment B), 5 early and 6 late recurrences (7 *E. coli*, 2 *S. saprophyticus*, 1 group B streptococcus, 1 enterococcus; treatment C) and 4 early and 4 late recurrences (6 *E. coli*, 1 *Enterobacter* spp., 1 group B streptococcus; treatment D). Treatment A was most effective in reducing rectal carriage of *E. coli* (rectal *E. coli* present on study d 4–6 in 38% treatment A, 91% treatment B, 97% treatment C and 87% treatment D recipients; A vs other 3 combined; p < 0.001). Parallel findings were noted for vaginal *E. coli* carriage (A vs other 3 combined, p < 0.001). Costs per pt were $US114 (treatment A), $US155 (treatment B), $US155 (treatment C) and $US131 (treatment D) [1990 costing]. Higher costs of treatments B and C were due to higher drug costs and higher charges for more frequent clinic FU visits (for recurrent UTIs, yeast vaginitis)	AEs were noted in 35%, 43%, 30% and 25% of treatment A, B, C and D recipients. 5 pts withdrew from the study due to AEs (3 treatment C, 1 treatment D, 1 treatment A). Symptomatic yeast vaginitis warranting treatment occurred in 6, 7, 12 and 5 pts receiving treatments A, B, C and D, respectively. No results of statistical testing were provided
Masterton and Bochsler[93] *(1995)*		
Amox/Clav 3.25 g × 1 dose (n = 144) Cotrim DS bid × 7 d (n = 135) [R/DB]	At 42 d after study entry, successful clinical responses were seen in 74% of Amox/Clav and 85% of Cotrim recipients (p ≤ 0.05). Corresponding rates for successful bacteriological responses were 64% and 80% (p ≤ 0.05). Mean times to resolution of symptoms, pooled and specifically dysuria, were similar in the 2 groups (p = NS for both)	AEs were reported by 15% and 12% of Amox/Clav and Cotrim recipients (p = NS). GI disturbances were predominant among Amox/Clav recipients and rashes among Cotrim recipients. 3 Amox/Clav and 9 Cotrim recipients were withdrawn prematurely from the study due to AEs. No results of statistical testing were provided
Leigh et al.[94] *(2000)*		
Cefd 100 mg bid × 5 d (n = 196) Cefac 250 mg tid × 5 d (n = 187) [R/DB]	At 5–9 d after therapy, the clinical CRs were 91.3% (Cefd) and 93.0% (Cefac) [p = NS]. Corresponding clinical CRs at the 4- to 6-wk post-therapy assessment were 90.8% and 94.7% (p = NS). Bacteriological eradication rates at 5–9 d after therapy (by pathogen) were 85.9% and 80.5%, and (by pt) were 84.7% and 79.7% in Cefd and Cefac recipients (both p = NS). At 4–6 wk post-therapy, the corresponding by pathogen and by pt eradication rates were 94.6% vs 90.7% and 94.0% vs 90.3% (both p = NS)	Treatment-emergent AEs occurred in 23% (Cefd) and 17% (Cefac) [p = 0.037]. Drug-related AE rates were 20.2% (Cefd) and 13.0% (Cefac) [p = 0.025]. Most AEs were referable to the GI and GU tracts. Diarrhoea was noted significantly more frequently in Cefd pts (9.4%) compared with Cefac pts (2.1%) [p < 0.001]
Nicolle et al.[95] *(1993)*		
Cefcan 300 mg bid × 3 d (n = 215) Amox 500 mg tid × 3 d (n = 94) [R/DB]	At the d 6–8 visit, clinical cure/improvement occurred in 69%/22% (Cefcan) and 71%/19% (Amox) [p = NS]. Bacteriological eradication occurred in 77% of pts in both groups (p = NS). At the d 28–35 visit, corresponding clinical outcomes occurred in 70%/8.8% and 65%/7.4% and bacteriological eradication in 70% and 65% (all p = NS). Bacteriological outcomes were not significantly different in the 2 groups vs *E. coli* and *S. saprophyticus*. Effectiveness of 3-d therapy decreased with increasing age at the d 6–8 visit (p = 0.001) and d 28–35 visit (p = 0.018). Resistance to the randomized drug was associated with lower CRs at the d 6–8 visit (p = 0.013) but not at the d 28–35 visit	AEs were noted in 35% of Cefcan and 33% of Amox recipients. Diarrhoea/nausea/headache were noted in 10%/5%/6% and 7%/5%/2% of Cefcan and Amox recipients, respectively. Premature discontinuation due to AEs occurred in 2 Cefcan and 1 Amox pt. No results of statistical testing provided

Continued next page

© 2008 Adis Data Information BV. All rights reserved.

Table I. Contd

Treatment [study design]	Clinical findings	Tolerability findings
Gupta et al.[96] *(2007)*		
Cotrim DS bid × 3 d (n = 148) Nitro 100 mg bid × 5 d (n = 160) [R]	At 30 d after therapy, the clinical CR was 79% in Cotrim and 84% in Nitro recipients (p = NS). At 5–9 d after therapy, the clinical CR after both treatments was 90%, while the bacteriological eradication rates were 91% (Cotrim) and 92% (Nitro) [both p = NS]. In Cotrim recipients, clinical cure and bacteriological eradication rates were lower in the 17 pts infected with nonsusceptible pathogens (41% and 65%) compared with the 131 with susceptible pathogens (84% and 97%) [both p ≤ 0.001]	AE rates were similar in the 2 groups
O'Connor et al.[97] *(2002)*		
TMP 'standard course' (n = 22) Nitro 'standard course' (n = 16) [R]	Bacteriological eradication occurred in 59% of TMP and 56% of Nitro recipients. Symptom resolution correlated well with bacteriological response	No mention of AEs
Talan et al.[98] *(2000)*		
Cipro 500 mg bid × 7 d (with/without an initial 400 mg IV dose) [n = 128] Cotrim DS bid × 14 d (with/without an initial dose of IV ceftriaxone 1 g) [n =127] [R/DB][i]	At 4–11 d post-therapy, bacteriological CRs were 99% (Cipro) and 89% (Cotrim) [p = 0.004]. Clinical CRs were 96% (Cipro) and 83% (Cotrim) [p = 0.002]. Resistance among *E. coli* was more frequently seen with Cotrim (18%) than Cipro (0) [p < 0.001]. Among Cotrim recipients, drug resistance was associated with greater bacteriological and clinical failure rates (p < 0.001 for both). Total costs per pt were $US531 and $US687 for Cipro and Cotrim, respectively. Total costs per cure were $US615 and $US770 for Cipro and Cotrim, respectively [1997 costing]	AEs in 24% of Cipro and 33% of Cotrim recipients

a 2 d post-treatment.

b p = 0.05.

c 6 wk post-treatment.

d 5–9 d post-treatment.

e 4–6 wk post-treatment.

f Postmenopausal women.

g The use of trade names is for product identification purposes only and does not imply endorsement.

h Women with recurrent UTIs.

i Macrocrystalline formulation.

j Acute uncomplicated pyelonephritis.

AE = adverse event; **Amox** = amoxicillin; **Amox/Clav** = amoxicillin/clavulanic acid; **Amp** = ampicillin; **bid** = twice daily; **Cefac** = cefaclor; **Cefadrox** = cefadroxil; **Cefcan =** cefcanel; **Cefd** = cefdinir; **Ceph** = cephalexin; **Cipro** = ciprofloxacin; **Cotrim** = cotrimoxazole (trimethoprim/sulfamethoxazole); **CR** = cure rate; **DB** = double-blind; **DS** = double strength; **EOT** = end of therapy; **ER** = extended-release; **Fosfo** = fosfomycin; **FU** = follow-up; **Gati** = gatifloxacin; **Gent** = gentamicin; **GI** = gastrointestinal; **GU** = genitourinary; **IB** = investigator-blinded; **IR** = immediate-release; **IV** = intravenous; **Nitro** = nitrofurantoin; **Norflox** = norfloxacin; **NS** = not significant; **O** = open label; **od** = once daily; **Oflox** = ofloxacin; **Pivmec** = pivmecillinam; **pt** = patient; **qid** = four times daily; **R** = randomized; **Tetra** = tetracycline; **tid** = thrice daily; **TMP** = trimethoprim; **UC** = urine culture.

© 2008 Adis Data Information BV. All rights reserved.

the same drug class or those already established as effective for the type of infection being evaluated. For evaluation of regimens of differing durations, the comparator should be either the same drug used in a conventional course of therapy or an agent for which the most experience has been accumulated. Statistical considerations require that sufficient numbers of patients for each clinical category be enrolled in each study arm such that the β error is ≤0.20 for detecting a real difference of ≥35% between the two test regimens. The α error should be ≤0.05 using a two-tailed test of significance (not one-tailed). Infections should be stratified and analysed by clinical category.

For acute uncomplicated cystitis, at the entry visit, a medical history and physical examination should be completed and urine culture, urinalysis, blood chemistries and haematology obtained. Telephone contact should be made 3–5 days after entry (if symptoms are reduced/absent, no testing is required; if symptoms are worse, the entry tests should be repeated). The entry visit procedures should be repeated 5–9 days after the end of therapy and the history/physical examination, urinalysis and urine culture at 4–6 weeks after the end of therapy. If the subject does not return for the 4- to 6-week follow-up visit, telephone contact should be attempted.

For acute uncomplicated pyelonephritis, the only differences from the study design just described include the addition of a blood culture at study entry and a repeat of all the study procedures at the day 3–5 visit (exception: no blood culture if entry culture was negative).

For uncomplicated cystitis, patients should be classified in terms of microbiological outcome (eradication or failure), clinical outcome (cure or failure) and a global (integrated) outcome. Microbiological results are generally considered more important than clinical results. Acute uncomplicated pyelonephritis has similar outcome parameters with a few caveats. Here, microbiological response is paramount. Failures should be classified as early (≤2 weeks post-treatment) or late (>2 weeks post-treatment), and as relapse or reinfection.

Expected clinical cure and microbiological eradication rates in uncomplicated cystitis for conventional regimens should exceed 85% at 5–9 days following the end of therapy. An improved or unchanged outcome, compared with that obtained with a licensed regimen, should be demonstrable by statistical analysis with a sample size of at least 150. Four- to 6-week follow-up data must be available for at least 50% of patients evaluated at 5–9 days post-therapy, with 60% of these patients being clinically cured and with bacteriuria counts below 10^3 cfu/mL. For short-course regimens, at least 75% of infections should end in clinical cure and microbiological eradication at the 5- to 9-day post-therapy visit. At least 50% of those seen at the day 5–9 post-therapy visit should be available at the 4- to 6-week post-therapy follow-up visit, and >65% of these patients should exhibit microbiological eradication and clinical cure.

Expected rates of clinical improvement and microbiological cure in acute uncomplicated pyelonephritis at 3–6 days post-initiation of therapy should exceed 95% and at 5–9 days post-therapy should exceed 80%. Four- to 6-week post-therapy follow-up should be available for at least 50% of patients evaluated at 5–9 days post-therapy and >60% of these patients should be microbiologically and clinically cured.

6.1 Empirical Therapy

Healthy, non-pregnant females presenting with frequency, dysuria and no vaginal symptoms have a 96% likelihood of having a UTI. Urinalysis and/or urine culture results would not alter this high likelihood of disease and thus empirical therapy would be appropriate.[100,101]

Making the decision based upon having one or more urinary symptoms is more sensitive but less specific than the process just described. This results in the probability of UTI dropping to 50%. Empirical therapy is still likely to be appropriate, but false-positive rates may increase and hence lead to inappropriate antimicrobial use.[100,101]

A cost-utility analysis of the management of uUTIs in women aged 18–50 years was conducted using a decision tree approach. The seven approaches evaluated included urinary nitrite and leukocyte esterase, 7 days of empirical therapy, complete urinalysis, urine culture and wait (office-based), urine culture and treatment (office-based), urine culture and wait (laboratory-based), and urine culture and

© 2008 Adis Data Information BV. All rights reserved.

treatment (laboratory-based). The urine culture and wait (office- or laboratory-based) approaches were more expensive and less effective. The urine culture and treatment (office- or laboratory-based) approaches had the greatest overall effectiveness but at a higher incremental cost. The most cost-effective strategy was to treat empirically for 7 days ($US71.52 per quality-adjusted life-month) [1995 costing]. If the antimicrobial cost were to exceed $US74.50 per month or the prior probability of UTI were to be less than 0.30, treatment guided by urinalysis results would be preferable. These are the only two changes that would modify the preferred strategy of empirical therapy. The cost utility of other strategies (vs empirical therapy) ranged from $US2964 to $US48 460 per quality-adjusted life-month. Thus, this study confirmed that empirical therapy (7 days) followed by therapy guided by complete urinalysis results were the two most cost-effective strategies.[102]

A double-blind, randomized, placebo-controlled trial in primary care was conducted in symptomatic New Zealand women aged 16–50 years with urinalysis results negative for pyuria and nitrites. Patients were randomized to receive either trimethoprim 300 mg once daily (n = 26) or placebo once daily (n = 33), both for 3 days. The median time to resolution of dysuria was 3 days in the trimethoprim group and 5 days in the placebo group (p = 0.002). On day 3, 74% and 24% of placebo and trimethoprim recipients, respectively, had ongoing dysuria (p = 0.0005). This difference lasted until day 7, at which point the corresponding proportions were 41% and 10% (p = 0.02). The median duration of constitutional symptoms (e.g. feverishness, shivers) was shortened by 4 days with trimethoprim (from 6 to 2 days; p = 0.02). On day 3, 46% of placebo and 0% of trimethoprim recipients had these symptoms (p = 0.04). The median durations of frequency, itching, abdominal pain and low back pain were not significantly different between the groups. Thus, although culture-negative, patients still responded to antimicrobial therapy. This justifies empirical therapy without dipstick urinalysis testing.[103]

A frequent question regarding recurrences of uUTIs is whether they are due to relapse (i.e. with the original uropathogen[s]) or reinfection (i.e. with new uropathogen[s]). An attempt has been made to answer this question through the use of molecular fingerprinting of the causative agent (*E. coli*) in a randomized placebo-controlled trial of pivmecillinam therapy. In pivmecillinam recipients (patients with negative urine cultures at the first follow-up visit), 77% had a relapse with the initial strain of *E. coli*, while 23% had reinfection with a new *E. coli* strain at the second follow-up visit. In patients with a positive urine culture result at the first follow-up visit, 80% had persistence of the initial *E. coli* strain, 15% had reinfection with a new *E. coli* strain and 5% had different *E. coli* strains at two follow-up visits (one had relapse followed by reinfection, one had persistence followed by reinfection). In the placebo recipients, most had *E. coli* at the first follow-up visit (96% persistence of the initial strain and 4% had different strains at the two follow-up visits [i.e. persistence followed by reinfection]). The fact that most UTIs at follow-up are caused by the initial strain supports the theory of a vaginal/rectal reservoir of uropathogens as well as the ability of uropathogens to persist within bladder epithelium despite appropriate therapy, constituting yet another reservoir for recurrent UTI.[104,105]

6.2 Laboratory Test Responses to Therapy

In a pilot trial conducted in 16 women with uUTIs, the pre-therapy and daily on-therapy results of laboratory tests were studied, with a focus on the differential results of those responding and not responding to therapy. In the 11 responders, the white blood cell count fell to normal values over 2–7 days, while in the 5 nonresponders, it never reached normal. In responders, bacterial counts fell to normal values over 8 hours to 5 days. In general, bacterial counts fell more rapidly than did the white blood cell count, especially during the initial 24 hours. In nonresponders, bacterial counts remained high or even increased over time. A reduction in white blood cell count by less than a factor of ten (or to normal) was the best predictor of therapy failure. The positive predictive values after 1, 2 and 3 days of therapy were 43%, 50% and 75%, respectively. Corresponding negative predictive values were 89%, 90% and 83% and agreement values were 69%, 75% and 81%. The following four general time courses were noted: (i) a rapid decline in white blood cell and bacterial counts by a factor of ≥10 within the initial

© 2008 Adis Data Information BV. All rights reserved.

24 hours pointed to success; (ii) static or increasing white blood cell and/or bacterial counts in the initial 24 hours pointed to failure; (iii) elevated white blood cell and/or bacterial counts on day 3 pointed to the need to continue therapy to prevent relapse; and (iv) a slow decline in white blood cell and/or bacterial counts was consistent with failure.[106]

6.3 Novel Approaches to Management

Empirical therapy can be provided with minimal physician intervention by non-physician practitioners and even via telephone. In selected patients, self-diagnosis and treatment of recurrent acute uUTIs is also a reasonable approach. As will be seen from the discussion in this section, these approaches can reduce unnecessary office visits and laboratory testing, increase adherence to treatment guidelines, increase convenience to patients and reduce costs. These goals can be achieved without increases in the frequencies of acute pyelonephritis or adverse events.[107-113] However, there are several contraindications to empirical therapy delivered by these means (table II).

The safety of phone management of presumed cystitis was evaluated by retrospective health records review (cohort sample) of women treated by one of three regional advise-and-appointment call centres of a large group-model managed care organization in northern California, USA. An adult female calling the centre with urinary complaints was evaluated by a trained registered nurse who determined her eligibility using an inclusion/exclusion criteria checklist. Of interest, exclusion criteria did not include older age, early pregnancy, diabetes or receipt of systemic corticosteroids. If the patient was eligible and consented to phone management, the chart form was forwarded to a physician who made the antimicrobial choice and signed the form. Antimicrobials included cephalexin 250 mg four times daily, cotrimoxazole double strength (DS; 800mg/160mg) twice daily, nitrofurantoin 100 mg four times daily and ciprofloxacin 250 mg twice daily (all for 3–7 days). In the case of early pregnancy, the choice was between 7 days of cephalexin or nitrofurantoin. Ciprofloxacin was only used in those at least 18 years old and non-pregnant.[107]

Table II. Contraindications to empirical therapy for urinary tract infections (UTIs) provided by non-physicians

Presence of a vaginal discharge
Prolonged symptoms
Severe/intolerable flank, side and/or abdominal pain
Inability to urinate for >3 hours
Body temperature 100.5°F (38°C), with flank pain, chills, nausea, and/or abdominal pain
Pregnancy
Recent urological surgery, procedure, catheterization
UTI during the previous 6 weeks
Frequent UTIs (at least three in the previous 12 months)
Any symptoms warranting urgent office-based assessment from the clinician

Of 4249 women managed for cystitis 'over the phone' during the 3-month study period, results were evaluable in 4177 (median age 39, range 16–97 years). Cephalexin, cotrimoxazole, nitrofurantoin and ciprofloxacin were used in 70.2%, 14.4%, 9.8% and 5.7% of patients, respectively. Safety of the phone management process was verified by the following results. No cases of sepsis or death occurred. No patient was hospitalized as a result of UTI complications. More serious urinary tract and gynaecological disorders occurred rarely. Diagnosis was made during the first medical encounter after phone treatment in 748 subjects (all within 6 weeks of phone treatment): UTI in 644 subjects (623 cystitis, 21 pyelonephritis), gynaecological infections in 61 subjects (46 bacterial vaginosis, 4 pelvic inflammatory disease, 2 herpes, 3 cervicitis, 6 miscellaneous) and noninfectious disorders in 43 subjects (31 urinary incontinence, 3 nephrolithiasis, 9 miscellaneous).[107]

A randomized controlled trial of office versus phone management of uUTIs in adult women was conducted in six primary care clinics in Michigan, USA. Women were randomized to receive care by phone or usual office-based care. Urinalysis/urine cultures were obtained from all patients and all were treated with 7 days of cotrimoxazole DS twice daily (nitrofurantoin 100 mg twice daily if sulfonamide-allergic). 201 women called in with symptoms consistent with UTI. However, 99 women were not eligible and 30 refused consent, so 72 were randomized (36 to each group). Of the 67 urine cultures obtained, 64% had significant growth (>10^3 cfu/mL) of one pathogen (*E. coli* in 79%). There were no differences between the groups in symptom scores (for dysuria, frequency, urgency and all three

© 2008 Adis Data Information BV. All rights reserved.

pooled) or satisfaction scores (for quality of care, outcome). Persistent symptoms at day 3 occurred in 61% and 56% of office-based and phone management patients, respectively (p-value not significant). Corresponding values on day 10 were 17% and 34% (p-value not significant). Thus, phone and office-based management were statistically indistinguishable in uUTIs in adult women.[108]

At Group Health of Puget Sound, Washington, USA, a telephone-based guideline was established for the management of uUTIs in 18- to 55-year-old women. A population-based, pre-post study with concurrent controls was conducted in 24 primary care clinics. If a patient met the criteria for telephone management, she was offered a routine clinic visit or no visit/no laboratory testing (telephone-based approach). A total of 3889 patients were eligible: 1761 in the 1-year pre-intervention phase, 1883 in the 1-year post-intervention phase (intervention clinics) and 245 in the 1-year post-intervention phase (control clinics). In the 1883 patients in the intervention clinics, 745 (40%) were managed only by phone triage by nursing staff. Comparing post- versus pre-guideline data, use of the telephone-based guideline reduced the proportions of patients having urinalysis performed (by 25%), having urine culture performed (by 27%) and having an initial office visit with a physician (by 33%). The proportion of patients receiving guideline-recommended antimicrobials rose 2.9-fold. There was no increase in adverse consequences after implementation such as follow-up visits for failures of therapy, pyelonephritis or sexually transmitted diseases. In a prospective analysis of the 2 control and 22 implementation clinics, use of the guideline reduced the proportion of patients having urinalysis performed by 20% and increased the proportion being prescribed a recommended agent by 53%. Non-significant changes occurred in the frequencies of urine cultures, routine clinic visits and adverse consequences. In the two control clinics, use of a recommended antimicrobial actually rose as well, from 10% to 35% ($p < 0.001$), perhaps as a result of communications with staff in intervention clinics or staff working in both clinic locations. Patient satisfaction was high (95% were satisfied with phone management and 85% would request phone management again and not a routine clinic visit if they were to develop another UTI).[109]

At the University of California at San Francisco, USA, use of a computer module to assist in the diagnosis and treatment of uUTIs in adult women without complicating factors was evaluated. Use of this module was validated against clinician diagnosis and urine culture results. In the validation study, 18 of 68 women (26%) were computer-directed therapy (CDT) eligible. In 17 of 18 women (94%), the clinician diagnosis was uUTI, while in one (6%), it was pyelonephritis. Two-thirds of CDT-eligible patients had positive urine culture results. Of the 89% who had phone follow-up, only 13% had persistent symptoms after 1 week, but in all cases further follow-up was not required. These results led to the implementation of CDT in the urgent care clinic as a management option, with patients receiving treatment without seeing a physician. Since implementation, 162 women have allowed evaluation by CDT and 56 women (35%) have been eligible for and received CDT. The vast majority (98%) found it easy to use and 95% would recommend it to friends and/or relatives. Only two women (4%) had a UTI-related return visit within 2 weeks.[110]

A retrospective medical record evaluation was performed of female patients with acute cystitis who were managed using a nurse-based and telephone-based algorithm. Between July 2004 and October 2006, 273 patients were so managed. Referral to urgent/emergency care, appointment for sexually transmitted disease screening, request for urinalysis without an office visit, and treatment without urinalysis, culture or referral occurred in 3.7%, 4.4%, 16.5% and 75.4% of patient contacts, respectively. Urinalyses and urine cultures were obtained in 17.6% and 5.9% of patient contacts, respectively. Over the subsequent 60 days, 16.8% were seen or made phone contact for recurrent or persisting urinary symptoms while, only 2.2% were diagnosed with pyelonephritis. Three-day regimens of cotrimoxazole (n = 197) or ciprofloxacin (n = 49) were the most frequently prescribed antimicrobials. Results demonstrated that a telephone-based nurse evaluation and treatment algorithm allowed for successful management of the majority of women with symptomatic uncomplicated lower UTIs.[111]

A decision aid comprising of four criteria (presence of burning or dysuria on urination, symptoms present for 1 day, presence of leukocytes [greater

© 2008 Adis Data Information BV. All rights reserved.

than trace] and presence of nitrites [any positive]) was validated in community-based practice in Canada. Canadian family physicians (n = 225) evaluated clinical findings, performed urine dipstick testing and prescribed treatment for 331 women with suspected cystitis. The sensitivity/specificity of the aid was determined using a positive urine culture result ($\geq 10^2$ cfu/mL) as the 'gold standard'. Three of the four decision variables were associated with having a positive urine culture result (all $p \leq 0.001$), while the fourth, symptoms for 1 day, was not ($p = 0.96$). Using a simplified decision aid (empirical antimicrobials without urine culture if at least two variables were present; otherwise, obtain a urine culture and await results) had a sensitivity of 80.3% and specificity of 53.7%. Had decision aid recommendations been followed, antimicrobial prescriptions, unnecessary prescriptions and urine cultures would have been reduced by 24%, 40% and 59%, respectively (all $p < 0.001$).[112] Such a decision aid lends itself to use in the types of alternative care programmes just described.

Some women with recurrent uUTIs are able to self-diagnose and self-treat on the basis of symptoms alone. In an uncontrolled trial conducted in adult women with recurrent UTIs (at least two in the previous 12 months), 176 patients enrolled and were followed-up for 2–12 months (mean follow-up duration was 8 months). After self-diagnosis, self-treatment was performed using short-course ofloxacin or levofloxacin. The accuracy of self-diagnosis was evaluated by evidence of a definite (urine culture-positive) or probable (sterile pyuria plus no alternative diagnosis) UTI based on the pretreatment urinalysis/urine culture. Women who self-diagnosed a UTI that was not microbiologically confirmed were evaluated for alternative diagnoses. Of the 28 patients who met these criteria, 25 were evaluated and in only one (4%) was an alternative diagnosis found.[113]

Eighty-eight of 172 women (51%) self-diagnosed at least one UTI. A total of 172 UTIs (approximately two per women) were self-diagnosed during the follow-up period. A uropathogen was found in 144 of 172 subjects (84%), while sterile pyuria was found in 19 subjects (11%) and no pyuria/bacteriuria was found in 9 subjects (5%). Ninety-four percent of self-diagnosed UTIs were true UTIs and required antimicrobial therapy. Clinical cure occurred in 92% and microbiological cure in 96% (at day 10) and 98% (at day 30). Minor adverse events occurred in 20% and did not lead to drug discontinuation. On the patient satisfaction instrument, responders answered positively to the six questions 94–100% of the time.[113]

6.4 Prophylaxis of Recurrent UTIs

Selected agents are recommended for the prevention of recurrent uUTIs (i.e. at least three UTIs in 12 months) and postcoital UTIs.[2] These include nitrofurantoin 50 mg (100 mg macrocrystalline formulation), cotrimoxazole (single-strength) and trimethoprim 100 mg, all administered once daily. Cotrimoxazole can be given as infrequently as thrice weekly (e.g. Monday-Wednesday-Friday). Fosfomycin can be given as 3 g once every 10 days. Methenamine hippurate should not be considered for long-term prophylaxis until large, well conducted, randomized, controlled trials clarify its role in those without known renal tract abnormalities.[114] Should 'breakthrough' UTIs occur, the fluoroquinolones can be used: ciprofloxacin 125 mg or norfloxacin 200–400 mg, both given once daily. Prophylaxis reduces the risk of a single clinical UTI recurrence over 12 months by 85% and a microbiologically confirmed UTI recurrence by 79% (number needed to treat = 1.85 for both endpoints). It also enhances the risk of vaginal/oral candidosis and adverse gastrointestinal effects (both being consistent with the usual adverse effects of oral antimicrobials) by 78% (number needed to harm = 13.5). Thus, utilizing prophylaxis in 14 at-risk women for 1 year will result in seven women having one less UTI that year at the cost of adverse events in one woman.[115] Older data suggested that there were no substantial differences between antimicrobials in terms of efficacy. However, recent data, gathered from a geographical area with high rates of cotrimoxazole and fluoroquinolone resistance among *E. coli*, have revealed substantial differences in success rates between cotrimoxazole, norfloxacin and nitrofurantoin prophylaxis. Respective success rates during the first 6 months of prophylaxis were 20%, 43% and 59% ($p = 0.06$). For prophylaxis extending beyond 6 months, respective success rates were 83%, 72% and 97% ($p = 0.046$). Another important finding was

© 2008 Adis Data Information BV. All rights reserved.

the correlation between poor adherence and failure of prophylaxis (for duration <6 months, $p < 0.0001$; ≥6 months, $p = 0.001$) and poor adherence with the development of resistance to the assigned agent (1 failure in 5 adherent patients vs 17 failures in 29 non-adherent patients).[116] It appears that the efficacy of daily versus postcoital administration is similar. Thus, for those women with sex-associated uUTIs, single-dose postcoital administration can be recommended.

Another potential approach to the prevention of recurrent UTIs includes the use of lyophilized immunoactive extracts of *E. coli* administered orally, either continuously or intermittently (i.e. loading regimen followed by booster regimens [e.g. *E. coli* 83972, OM-89]).[117,118] Selected probiotics (*Lactobacillus rhamnosus* GR-1 and *L. reuteri* RC-14 [previously known as *L. fermentum* RC-14] and, perhaps, *L. casei shirota* and *L. crispatus* CTV-05) administered intravaginally and orally has produced encouraging results in several studies. In contrast, *Lactobacillus* GG has been ineffective. The potential for probiotic therapy to induce *Lactobacillus* infections in reasonably healthy individuals is vanishingly low.[119,120] It is important to realise that these positive results are limited to only a few strains of lactobacilli and that this is not a genus-wide effect. At present, these biological agents are not widely available and, in any case, further research data are needed before widespread use of biologicals for this indication can be recommended.

In older women, intravaginal estrogen, even in the absence of signs and symptoms of vaginal estrogen deficiency, reduces the risk of recurrent UTIs. The efficacy of estrogens appears to be greater with intravaginal compared with systemic administration (i.e. oral and transdermal routes). Administration via the intravaginal route (using pill, cream and ring formulations) also avoids the systemic adverse effects seen with the systemic formulations.[121,122]

7. Treatment Guidelines

7.1 Sweden (1990)

In Sweden, pivmecillinam, cotrimoxazole, nitrofurantoin and cephalosporins (cefadroxil, cephradine) are first-line agents for uUTI. The corresponding recommended durations of therapy are 7, 3, 4–6 and 7 days, respectively. In addition, diagnostic testing (except urine culture in uUTI) is recommended in all individuals suspected of having a UTI: nitrite, leukocyte esterase, urinary sediment, C-reactive protein.[123]

7.2 Spain (2003)

In non-pregnant women, fosfomycin (3 g) and three fluoroquinolones (ciprofloxacin 100–250 mg twice daily, norfloxacin 400 mg twice daily and ofloxacin 200 mg twice daily) are considered first-line agents for uUTI in Spain. Amoxicillin/clavulanic acid (250 mg three times daily) and cefuroxime axetil (250 mg twice daily) are alternative agents. Agents such as cotrimoxazole, trimethoprim and nitrofurantoin are not considered appropriate (the latter agent because of its adverse event profile and multiple daily administration requirement). The recommended durations of therapy for the first-line and alternative-choice agents are 1 (single-dose), 3, 3, 3, 5 and 3–5 days, respectively.[32,124]

7.3 USA (1999)

Current guidelines for the treatment of acute uUTI (cystitis and pyelonephritis) in the US have been provided by the Infectious Diseases Society of America (IDSA).[125] In patients with antimicrobial allergy issues or where recent urine culture and sensitivity data are available, the recommendation is to treat accordingly. In other patients, empirical therapy is justified. If patients have one or more risk factors for antimicrobial resistance (e.g. current/recent use of cotrimoxazole or [an]other agent[s], recent hospitalization or recurrent UTIs during the previous year), the recommendation is to use one of the following regimens: fluoroquinolone for 3 days (if severe symptoms); nitrofurantoin for 7 days (if mild-moderate symptoms); or single-dose fosfomycin. Ciprofloxacin and levofloxacin are the fluoroquinolones of choice. If local cotrimoxazole resistance rates among uropathogens (*E. coli*) exceed 10–25%, the same three regimens are recommended. Otherwise, cotrimoxazole for 3 days is the empirical regimen of choice. β-Lactams produce inferior bacteriological cure rates and higher recur-

© 2008 Adis Data Information BV. All rights reserved.

rence rates compared with the traditional first-line agents listed here, even against susceptible pathogens, and hence they should not be considered first-line agents. In patients with acute pyelonephritis who can be safely treated as outpatients, the first- and second-line agents are the fluoroquinolones (for 7 days) and cotrimoxazole (for 7–14 days), respectively. If Gram-positive pathogens are noted, amoxicillin therapy should be added to both regimens. Regimens should be modified, depending on the clinical results and results of urine culture and susceptibility testing.[125]

7.4 EU (2001)

Current guidelines for acute uncomplicated cystitis and pyelonephritis in the EU have been provided by the European Association of Urology.[9] Suitable patient types are similar to those in the IDSA guidelines except for the omission of postmenopausal women. Urine culture and sensitivity testing is generally not necessary since the causative organism(s) and its/their antimicrobial susceptibilities are well known and predictable. Final test results will also not be available until symptoms have responded (partially to completely). If symptoms are atypical, symptoms do not resolve, or the infection recurs within 2 weeks, urine culture and sensitivity testing is warranted.

Recommendations are to use 3 days of therapy, although specific agents suitable for use throughout Europe are not named. Antimicrobial choice depends on local susceptibility patterns. Cotrimoxazole in a 3-day regimen or trimethoprim in a 5- to 7-day regimen are first-line agents if the trimethoprim resistance rate among *E. coli* is <10%. Fluoroquinolones in 3-day regimens are not first-line agents because of their cost, unless a high trimethoprim resistance rate (>10%) mandates their use. If used, they should be agents primarily renally excreted in unchanged form (ciprofloxacin 250 mg twice daily or 500 mg extended release once daily, levofloxacin 250 mg once daily, norfloxacin 400 mg twice daily or ofloxacin 200 mg twice daily). β-Lactams are less effective than fluoroquinolones, cotrimoxazole and trimethoprim, and should, in general, not be used. An exception to this statement is cefpodoxime 100 mg twice daily for 3 days. Also, pivmecillinam 200 mg twice daily in a 7-day regimen is a popular agent in the Nordic countries. The use of nitrofurantoin (50–100 mg thrice daily or 100 mg twice daily of the macrocrystalline form) is felt to need more study, although, if it is used, a 5- to 7-day regimen is recommended. Single-dose fosfomycin (3 g) is also an alternative, although more comparative trials with 3-day fluoroquinolone and cotrimoxazole (or trimethoprim) regimens are necessary before it could be preferred to the latter. Infection known to be caused by *S. saprophyticus* may respond better to 7 days of therapy with all agents, but data are sparse.

In acute uncomplicated pyelonephritis, evaluation of the upper urinary tract via excretory urogram, ultrasound, computed tomography, plain radiograph, etc. is warranted if symptoms resolve but recur within 2 weeks or if the patient is still febrile after 72 hours of therapy. In the latter instance, presence of a renal or perinephric abscess needs to be ruled out. Recommended agents for outpatient management of mild disease include oral fluoroquinolones or second- or third-generation cephalosporins for 7–10 days. If Gram-positive organisms are noted on the Gram-stain, an aminopenicillin/β-lactamase inhibitor combination can be substituted. Alternative agents to the fluoroquinolones and cephalosporins include an aminopenicillin/β-lactamase inhibitor combination or an aminoglycoside.

8. Adherence to Treatment Guidelines

8.1 Sweden

A survey was conducted in 2000 and 2002 in five Swedish counties to evaluate adherence to the treatment guidelines promulgated in 1990. There were 491 and 398 lower UTIs evaluated in 2000 and 2002, respectively. Utilization rates of first-line agents (cotrimoxazole, pivmecillinam, nitrofurantoin and cephalosporins) in 2000 and 2002 were 77% and 86%, respectively. From 2000 to 2002, utilization of fluoroquinolones fell from 21% to 13% ($p = 0.001$) and that of nitrofurantoin rose from 3% to 6% ($p = 0.036$), both being evidence of improved adherence. In addition, utilization of 3-day trimethoprim therapy rose from 1% to 12% ($p < 0.001$), another positive finding. However, the use of prolonged regimens was still problematic (65% of regimens were for 7 days and 79% for

© 2008 Adis Data Information BV. All rights reserved.

7–10 days). A major barrier to adherence is the available antimicrobial package sizing in Sweden, which is not congruent with the guidelines. Another major problem is the prescribing of antimicrobials to patients with negative laboratory test results. This phenomenon suggests that financial resources are being wasted, since laboratory test results do not appear to influence antimicrobial prescribing. The lack of adherence to the laboratory testing guideline (since individual tests were obtained in 9–76% [mean 40%] of appropriate individuals) may have mitigated this waste to some extent.[123]

8.2 Israel

Investigators evaluated the adherence of prescribers to uUTI guidelines in adults in an Israeli managed care organization (Leumit Health Fund)[57] serving over 1.6 million adult insurees over the period from July 2000 to June 2002 (64 236 index physician/patient encounters). Nitrofurantoin and cotrimoxazole were prescribed in 18.5% and 17.0%, respectively, yielding a crude adherence rate of 35.6%. Adherence rates by specialty were 54.2% (urology), 36.5% (gynaecology), 35.4% (non-specialty), 34.1% (family practice), 31.7% (internal/occupational medicine) and 24.7% (paediatrics). By logistic regression analysis, significant parameters affecting adherence included physician specialty (where urology [OR 2.83], gynaecology [OR 1.99] and non-specialty [OR 1.23] were more adherent than the family practice category [$p < 0.001$]) and medical school attended (where Techunion [OR 2.43], Eastern European [OR 1.94], Hebrew University Jerusalem [OR 1.53] and other [OR 1.37] graduates were more adherent than a group of Western European, US and Australian graduates [$p < 0.001$]).[100]

In another study using the same managed care organization database (from January 2001 to June 2002), 7738 index physician/patient encounters were evaluated. Cotrimoxazole (25.8%) and nitrofurantoin (14.7%) were the two most-frequently prescribed agents (40.5% adherence to guidelines). Fluoroquinolones and cephalosporins were each utilized in 22.8% of patients. Upon multivariate analysis, the following four factors were found to significantly impact the appropriateness of therapy:[126]

1. physician site of training ($p < 0.00001$; Romanian-trained, as opposed to Israeli-trained, physicians were less appropriate prescribers; OR 0.40; $p < 0.008$);
2. type of physician ($p < 0.007$; internists, as opposed to general practitioners, were less-appropriate prescribers; OR 0.36; $p < 0.002$);
3. location of practice ($p < 0.00001$; prescribers in northern and southern Israel, compared with central Israel, were less-appropriate prescribers; OR 0.29);
4. the patient age category ($p < 0.011$; prescribing was less appropriate in 18- to 44-year-old patients compared with patients ≥45 years old; OR 0.87).

8.3 Spain

A cross-sectional survey of antimicrobial use for UTI was performed in the emergency rooms of ten hospitals from different regions of Spain from March 2003 to March 2004. Of 3797 acute UTIs, 1366 were uUTIs in non-pregnant women. Antimicrobial use was as follows: ciprofloxacin (33.4%), amoxicillin/clavulanic acid (27.8%), fosfomycin (15.9%), norfloxacin (8.2%), cefuroxime axetil (4.5%), levofloxacin (3.8%), cotrimoxazole (2.3%), ofloxacin (1.2%) and others (3.3%). First-line agents (fosfomycin, ciprofloxacin, ofloxacin, norfloxacin) were prescribed in 51% of patients, alternative-choice agents (amoxicillin/clavulanic acid, cefuroxime axetil) in 37% and inappropriate agents (cotrimoxazole, levofloxacin, others) in 11%. The major finding in this trial was overuse of alternative-choice antimicrobials, not the more common finding of overuse of inappropriate agents seen in trials conducted in other countries. However, the recommended agents in Spain are quite different from those recommended elsewhere (see section 7.2), and this probably explains this finding.[124]

8.4 USA

The Mayo Clinic (Scottsdale, Arizona, USA) assessed adherence to evidence-based guidelines for the diagnosis and treatment of uUTI through a retrospective review of medical records of women treated in 2005 (International Classification of Diseases [ICD]-9 code 599.0). Sixty-eight women comprised the study database. Essential medical history and physical examination findings had been recorded for

© 2008 Adis Data Information BV. All rights reserved.

most patients. Documentation of sexually transmitted disease risk varied between residents and attending physicians, and was affected by patient age. A dipstick urinalysis and urine culture and sensitivity were ordered in 84% and 76%, respectively. Eighty percent of patients with positive urinalysis results also had a urine culture and sensitivity performed. Cotrimoxazole was the drug-of-choice in only 38%. Sixty-one percent of cotrimoxazole and ciprofloxacin prescriptions were appropriately written for a duration of 3 days. The cotrimoxazole resistance rate for *E. coli* was 6% (n = 35 isolates). No therapy was changed in any patient with uUTI as a result of the results of urine culture and sensitivity testing. Less than 25% of patients received appropriate empirical treatment (3 days of cotrimoxazole) in this patient population.[127]

In 1995, a staff-model managed care organization adopted the Institute of Clinical Systems Integration uncomplicated cystitis guidelines, and implementation and adherence were assessed in five primary care clinics. In a pre-post study design, data were collected on 201 women with uncomplicated cystitis who were treated over the 3 months before guideline implementation and 241 who were treated over the 3 months following implementation. The four key guideline elements were as follows: (i) use of 3-day treatment regimens; (ii) avoidance of urine cultures; (iii) use of only recommended agents; and (iv) coordination of care primarily by nursing staff. Before guideline implementation, no case fulfilled all four elements (12% fulfilled three elements), while after implementation 32% fulfilled all four elements (60% fulfilled three elements) [$p < 0.001$]. Use of 3-day therapies rose from 28% pre-implementation to 52% post-implementation ($p < 0.001$). Use of urine cultures fell from 70% (pre) to 30% (post) [$p < 0.001$]. Use of only recommended agents rose to a non-significant extent (from 83% pre to 86% post). The proportion of eligible patients with care primarily coordinated by nursing staff rose from 21% (pre) to 78% (post) [$p < 0.001$]. Use of 3-day therapies rose non-significantly with physicians (from 29% pre to 39% post), but rose significantly with nurses (from 23% pre to 58% post) [$p < 0.001$]. Avoidance of urine cultures non-significantly improved with physicians (from 33% pre to 41% post), but significantly improved with nurses (from 18% pre to 74% post) [$p < 0.001$]. Guideline implementation was not associated with increases in hospital admissions, emergency room visits, follow-up office visits or repeat antimicrobial courses (a surrogate for antimicrobial failure). Cystitis care costs fell by 35% after implementation, the major savings occurring from reduced personnel and antimicrobial costs, and avoidance of the costs of urine cultures.[128]

Using 1996–2001 data from the National Hospital and Ambulatory Medical Care Surveys, a cross-sectional data analysis was performed, evaluating the use of medical services in the US by adult women with uUTIs. The major goal was to examine prescribing practices for uUTIs and adherence to established guidelines. uUTI cases numbered 2339. The most frequently prescribed agents were cotrimoxazole (29.8% of visits), ciprofloxacin (24.2%), nitrofurantoin (18.8%) and other fluoroquinolones (11.2%). Despite the IDSA guidelines promulgated in 1999, the prevalence of cotrimoxazole use did not change (OR 0.89; 95% CI 0.60, 1.30; $p = 0.53$), while that of ciprofloxacin (which is not a first-line agent) increased significantly (OR 1.75; 95% CI 1.11, 2.75; $p \leq 0.016$). The prevalence of use of amoxicillin, nitrofurantoin and other fluoroquinolones also did not change over time. These results were unchanged, even after adjusting for confounders. The prevalence of use of 'urine tests' also did not change over time ($p = 0.096$), despite the downplaying of urine testing in the guidelines. Other interesting results also emerged. Providers in hospital clinics were more likely than those in private practice to prescribe cotrimoxazole (54.7 vs 27.6%, respectively; $p < 0.001$). The opposite phenomenon occurred with ciprofloxacin prescribing (24.8% [private] vs 18.1% [hospital]; $p = 0.038$). Patients aged <50 years were more likely to be prescribed cotrimoxazole (36.1%) than those aged >50 years (22.9%; $p = 0.001$). Whites were less likely to be prescribed cotrimoxazole (27.8%) than non-Whites (40.8%; $p = 0.015$). General medicine physicians were more likely to prescribe cotrimoxazole (32.4%) compared with other physician types (21.5%; $p = 0.01$). Obstetricians/gynaecologists were more likely to prescribe nitrofurantoin (39.1%) compared with other physician types (16.6%; $p < 0.001$). Race had no significant effect on ciprо-

© 2008 Adis Data Information BV. All rights reserved.

floxacin or nitrofurantoin prescribing. Lastly, self-paying patients were more likely to be prescribed cotrimoxazole (42.4%) than patients with insurance (27.9%; p = 0.047).[129]

9. Pharmacoeconomics

Investigators evaluated the economic impact of physician non-adherence to treatment guidelines, using a large Israeli managed care organization database previously described (see section 8.2).[106,107] In the timeframe of January 2001 to June 2002, there were 7738 physician/patient interactions involving uUTIs. The top two agents utilized were those in the guideline (cotrimoxazole in 25.8%, nitrofurantoin in 14.7%), producing an adherence rate of 40.5%. However, five inappropriate drugs (ciprofloxacin, ofloxacin, fosfomycin, cefuroxime axetil and cephalexin) constituted 49.9% of utilization and 82.6% of total antimicrobial costs. The cost of treatment exceeded the expected cost (i.e. had cotrimoxazole or nitrofurantoin been used) in 70% of patients.[130]

In an extension to the previous study,[130] investigators assessed the epidemiology and economic consequences of longer-than-recommended empirical therapy. Adherence rates to treatment duration guidelines were 22.2% for nitrofurantoin (5 days), 4.1% for ofloxacin (3 days) and 3.4% for cotrimoxazole (3 days). This resulted in an 8.7% crude adherence rate. The vast majority of cases of nonadherence were due to prolonged durations of therapy (e.g. most prescriptions for cotrimoxazole were for 5, 7 or 10 days; for nitrofurantoin were for 7 or 10 days; for ofloxacin were for 5, 7 or 10 days). The mean excess expenditures in all cases were $US5.86 and $US3.43 [2003 costing] for ofloxacin and nitrofurantoin, respectively. This translated to an annual loss to the organization of approximately $US19 000. If extrapolated to the entire country (6.5 million), this loss becomes $US190 000 per annum.[131,132]

However, the economies of pharmacotherapy can be altered by the presence of antimicrobial resistance. In a decision analysis model of costs as a function of cotrimoxazole resistance rates, treatment costs increased as the resistance rate increased: with 0%, 10%, 20% and 30% cotrimoxazole resistance rates, the costs of cotrimoxazole therapy were $US92, $US99, $US106 and $US113, respectively [2000 costing]. In fact, when the mean cost of fluoroquinolone treatment was $US107 and the cotrimoxazole resistance rate was 22%, fluoroquinolones became more cost-effective treatment than cotrimoxazole.[133]

10. General Treatment Recommendations

The Cochrane Collaboration in 2005 conducted a meta-analysis examining 3 days of antimicrobial therapy compared with ≥5 days of therapy in terms of symptomatic response and elimination of bacteriuria in uUTIs in non-pregnant, adult women. The study database included 32 clinical trials (9605 patients). In terms of symptomatic failure rates, there were no significant differences between the two groups, either short-term (RR 1.06) or long-term (RR 1.09). In terms of bacteriological failure rates, 3 days was less effective than ≥5 days at short-term follow-up (only when the same antimicrobials were used in both arms of each trial; RR 1.37; p = 0.01). This difference was still significant at long-term follow-up (RR 1.43; p = 0.0002). Adverse events were significantly less frequent with 3 days compared with ≥5 days of therapy (RR 0.83; p = 0.001). In summary, both therapy durations produced similar symptomatic cure rates, with ≥5 days of therapy producing increased bacteriological cure rates compared with 3 days of therapy, albeit at the expense of more adverse events. The authors felt that since uUTI is primarily an issue of symptoms and not long-term tissue damage (where, for the latter, bacteriological cure would be more important), 3 days of therapy is quite acceptable.[134]

In general, the usual duration of therapy for nitrofurantoin and the β-lactams is 7 days, while that for cotrimoxazole, trimethoprim (use only in the sulfonamide-allergic) and the fluoroquinolones is 3 days. Usual dosage regimens for these agents are provided in table III.[135,136]

If cotrimoxazole resistance rates are below 10%, cotrimoxazole can be a first-line empirical agent. If cotrimoxazole resistance rates are 10% to ≥20%, the fluoroquinolones should be considered first-line.[135] Nitrofurantoin and fosfomycin are not considered first-line empirical agents because of their narrow

© 2008 Adis Data Information BV. All rights reserved.

Table III. Dosage recommendations for uncomplicated urinary tract infections[135,136]a

Drug	Dosage
Penicillins	
Amoxicillin	250–500 mg tid × 3–10 days
Amoxicillin/clavulanic acid	250–500 mg bid-tid × 3–10 days
Cephalosporins	
Cephalexin	250–500 mg qid × 3–10 days
Cephradine	250–500 mg qid × 3–10 days
Cefaclor	250–500 mg tid × 3–10 days
Cefadroxil	500–1000 mg bid × 3–10 days
Cefuroxime axetil	125–250 mg bid-tid × 3–10 days
Fluoroquinolones	
Ciprofloxacin	250 mg bid × 3 days
ER formulation (Cipro®XL)	500 mg qd × 3 days
Levofloxacin	250 mg qd × 3 days
Norfloxacin	400 mg bid × 3 days
Miscellaneous	
Cotrimoxazole	One DS tablet bid × 3 days
Trimethoprim	200 mg bid × 3 days
Nitrofurantoin	50–100 mg qid × 7 days
Macrocystalline formulation (Macrodantin®)	100 mg bid × 7 days
Fosfomycin	3 g × 1 dose

a All agents to be taken orally. Regimens assume normal renal function is present.

bid = twice daily; **DS** = double strength; **ER** = extended release; **qid** = four times daily; **tid** = three times daily.

spectra of activity and relative paucity of data compared with the fluoroquinolones.[135]

Single-dose therapy of all drugs except fosfomycin is not recommended because of suboptimal cure rates compared with 3- to 7-day regimens (e.g. for fluoroquinolones, 3-, 5- and 7-day regimens provide statistically equivalent results that are superior to those of single-dose therapy; see also table I).[74]

Single-dose therapy of uUTIs with cephalosporins has been recommended in young to middle-aged women (e.g. 2 g of cephradine or cefaclor orally, or intramuscular cefamandole 1 g or cefuroxime axetil 1.5 g). However, single-dose therapy with cephalosporins appears to be less effective than that with amoxicillin or cotrimoxazole, with bacteriological eradication rates as low as 30% at 14–28 days post-therapy.[136] Even 3- to 10-day treatment courses with oral cephalosporins are not considered equivalent to those with cotrimoxazole, the fluoroquinolones or nitrofurantoin, with suboptimal clinical and bacteriological cure rates and higher recurrence rates.[136] Similar considerations apply to the penicillins.

When treating patients with renal impairment, the approach to using several antimicrobials is altered. Most importantly, nitrofurantoin should not be used when the estimated/measured creatinine clearance falls below 40 mL/min. Not only will inadequate drug concentrations be achieved in the urine in individuals with creatinine clearance <40 mL/min, systemic drug accumulation will also occur, predisposing to neurological, pulmonary, gastrointestinal and other toxicities. For UTIs (only), cotrimoxazole dosage regimens should not be altered. For β-lactams and fluoroquinolones, dosage regimen adjustment (reduced dosage, prolonged dose administration interval, or both) should be performed as recommended on a drug-specific basis.[2]

An important issue regarding antimicrobial resistance is the ability of *in vitro* susceptibility data to predict clinical outcome. With nitrofurantoin and fosfomycin, *in vitro* susceptibility data are based on achievable urinary drug concentrations. With other agents, *in vitro* susceptibility data are based on achievable serum drug concentrations, not urinary drug concentrations. This may be an important consideration when achievable urinary drug concentrations far exceed those in serum. A recent article describes a successful outcome of fluoroquinolone therapy of a fluoroquinolone-resistant pathogen.[137] This suggests a potential need to alter fluoroquinolone breakpoints for uropathogens during uUTIs. If this were to occur, the epidemiology of fluoroquinolone resistance would, obviously, be dramatically altered in this infection type. With pyelonephritis, serum and urinary drug concentrations are both important in light of the degree of tissue injury and fluoroquinolone breakpoints should not be altered in this entity. However, further research is required before this approach can be recommended.

Available data suggest that the correlations of serum versus urinary drug concentrations with clinical and/or bacteriological cure in uUTIs may be class specific. For the tetracyclines, urinary drug concentrations, not those in serum, better predict clinical cure.[138] In contrast, for cotrimoxazole, serum drug concentrations better predict clinical and

© 2008 Adis Data Information BV. All rights reserved.

bacteriological cure, despite the high degree of urinary excretion of both drug components.[89]

Ciprofloxacin, ofloxacin, nitrofurantoin and cotrimoxazole are considered compatible with breast feeding. Although compatible, the fluoroquinolones are not frequently recommended because of the arthropathy seen in animals. With nitrofurantoin, it should be avoided in those at risk for glucose-6-phosphate dehydrogenase deficiency (especially in those of Mediterranean and African ancestry).[139]

11. Conclusions

uUTIs are common in adult women across the entire age spectrum. The majority of uUTIs are caused by *E. coli* (70–95%), with *P. mirabilis*, *Klebsiella* spp., and *S. saprophyticus* accounting for the majority of the balance of uropathogens. If clinical signs and symptoms consistent with uUTI are present (e.g. dysuria, frequency, back pain or costovertebral angle tenderness) and there is no vaginal discharge or irritation present, the likelihood of uUTI is greater than 90–95%. Laboratory testing (i.e. urinary nitrites, leukocyte esterase, culture) is not necessary in this circumstance and empirical treatment can be initiated. The ever-increasing incidence of antimicrobial resistance of the common uropathogens in uUTIs has been and is a continuing focus of intensive study. Resistance to cotrimoxazole has made the empirical use of this drug problematic in many geographical areas and, in a few countries, uropathogen resistance rates to the fluoroquinolones now exceed 10–25%. Management of uUTIs can frequently be triaged to non-physician healthcare personnel without adverse clinical consequences, resulting in substantial cost savings. It can be anticipated that the optimal approach to the management of uUTIs will change substantially in the future as a consequence of antimicrobial resistance.

Acknowledgements

No sources of funding were used to assist in the preparation of this review. The author has no conflicts of interest that are directly relevant to the content of this review.

Addendum in Proof

A recent study has addressed within-household (humans and pets) transmission of *E. coli* as a risk factor for UTI. Faecal samples from 228 subjects (152 humans [5 with acute UTI] and 76 pets) in 63 households were processed to identify unique *E. coli* clones. Patterns of strain sharing (i.e. presence of a single clone in multiple individuals) were also assessed. Of 335 *E. coli* clones, 90 (27%) were recovered from multiple hosts (up to 11 per clone). Within-household strain sharing occurred in 68% of households, including three of five households in which one member had a UTI. Within-household strain sharing was more frequent than across-household sharing (27% vs 0.8% of potential sharing pairs, respectively [$p < 0.001$]). Such strain sharing increased with increasing household size ($r^2 = 0.93$; $p < 0.001$) and varied by host pair type (pet-pet 58%, human-human 31%, human-pet 17%). Sex partners shared strains more commonly than did other adults (31% vs 7% of pairs, respectively; $p = 0.08$) but accounted for only 12% of within-household strain sharing. It can be concluded that within-household sharing of *E. coli*, including those with a member having a UTI, is common and can involve any combination of humans and pets. Identification of the mechanism(s) underlying this phenomenon may lead to more preventative measures against UTI.[140]

A novel type of fimbriae has been identified (type 3), which appears to play a role in biofilm formation by different Gram-negative urinary pathogens (catheter-associated UTI [CAUTI] strains of UPEC, *Citrobacter freundii*, *C. koseri*, *K. pneumoniae*, *K. oxytoca*). Whether or not non-CAUTI strains of Gram-negative uropathogens express this fimbrial type is unknown.[141]

References

1. Richards DA, Toop LJ, Chambers ST, et al. Antibiotic resistance in uncomplicated urinary tract infection: problems with interpreting cumulative resistance rates from local community laboratories. New Zealand Med J 2002 Jan 25; 115 (1146): 12-4
2. Car J. Urinary tract infections in women: diagnosis and management in primary care. BMJ 2006 Jan 14; 332 (7533): 94-7
3. Czaja CA, Hooton TM. Update on acute uncomplicated urinary tract infection in women. Postgrad Med 2006 Jun-Jul; 119(1): 39-45
4. Foxman B, Brown P. Epidemiology of urinary tract infections: transmission and risk factors, incidence, and costs. Infect Dis Clin North Am 2003 Jun; 17 (2): 227-41
5. Bass 3rd PF, Jarvis JA, Mitchell CK. Urinary tract infections. Prim Care Clin 2003 Mar; 30 (1): 41-61
6. Ki M, Park T, Choi BY, et al. The epidemiology of acute pyelonephritis in South Korea, 1997-1999. Am J Epidemiol 2004; 160: 985-93

© 2008 Adis Data Information BV. All rights reserved.

7. Laupland KB, Ross T, Pitout JD, et al. Community-acquired urinary tract infections: a population-based assessment. Infection 2007 Jun; 35 (3): 150-3
8. Hooton TM. The current management strategies for community-acquired urinary tract infection. Infect Dis Clin North Am 2003 Jun; 17 (2): 303-32
9. Naber KG, Bergman B, Bishop MC, et al. EAU guidelines for the management of urinary and male genital tract infections. Eur Urol 2001; 40: 576-88
10. Ferry SA, Holm SE, Stenlund H, et al. The natural course of uncomplicated lower urinary tract infection in women illustrated by a randomized placebo controlled study. Scand J Infect Dis 2004; 36 (4): 296-301
11. Godaly G, Svanborg C. Urinary tract infections revisited. Kidney Int 2007 Apr; 71 (8): 721-3
12. Bullitt E, Makowski L. Structure polymorphism of bacterial adhesion pili. Nature 1995; 373: 164-7
13. Bergsten G, Wullt B, Schembri MA, et al. Do type 1 fimbriae promote inflammation in the human urinary tract? Cell Microbiol 2007 Jul; 9 (7): 1766-81
14. Ulett GC, Valle J, Beloin C, et al. Functional analysis of antigen 43 in uropathogenic *Escherichia coli* reveals a role in long-term persistence in the urinary tract. Infect Immunol 2007 Jul; 75 (7): 3233-44
15. Zasloff M. Antimicrobial peptides, innate immunity, and the normally sterile urinary tract. J Am Soc Nephrol 2007; 18: 2810-6
16. O'Brien K, Hillier S, Simpson S, et al. An observational study of empirical antibiotics for adult women with uncomplicated UTI in general practice. J Antimicrob Chemother 2007 Jun; 59 (6): 1200-3
17. Nys S, van Merode T, Bartelds AI, et al. Urinary tract infections in general practice patients: diagnostic tests versus bacteriological culture. J Antimicrob Chemother 2006 May; 57 (5): 955-8
18. McIsaac WJ, Low DE, Biringer A, et al. The impact of empirical management of acute cystitis on unnecessary antibiotic use. Arch Int Med 2002 Mar 10; 162 (5): 600-5
19. Bent S, Nallamothu BK, Simel DL, et al. Does this woman have an acute uncomplicated urinary tract infection? JAMA 2002 May; 287(20): 2701-10
20. Batchelor BI, Crook DW, Jones T, et al. Impact of guidelines for the diagnosis of urinary tract infection on trimethoprim susceptibility of *Escherichia coli*. J Antimicrob Chemother 2002 Jan; 49 (1): 223-4
21. Gupta K, Scholes D, Stamm WE. Increasing prevalence of antimicrobial resistance among uropathogens causing acute uncomplicated cystitis in women. JAMA 1999 Feb 24; 281 (8): 736-8
22. Karlowsky JA, Kelly LJ, Thornsberry C, et al. Susceptibility to fluoroquinolones among commonly isolated gram-negative bacilli in 2000; TRUST and TSN data for the United States. Int J Antimicrob Agents 2002; 19: 21-31
23. Gupta K, Sahm DF, Mayfield D, et al. Antimicrobial resistance among uropathogens that cause community-acquired urinary tract infections in women: a nationwide analysis. Clin Infect Dis 2001 Jul 1; 33 (1): 89-94
24. Karlowsky JA, Hoban DJ, Decorby MR, et al. Fluoroquinolone-resistant urinary isolates of *Escherichia coli* from outpatients are frequently multidrug resistant: results from the North American Urinary Tract Infection Collaborative Alliance-Quinolone Resistance study. Antimicrob Agents Chemother 2006 Jun; 50 (6): 2251-4
25. Kiffer CR, Mendes C, Oplustil CP, et al. Antibiotic resistance and trend of urinary pathogens in general outpatients from a major urban city. Int Braz J Urol 2007 Jan-Feb; 33(1): 42-49
26. Goldstein FW. Antibiotic susceptibility of bacterial strains isolated from patients with community-acquired urinary tract infections in France. Eur J Clin Microbiol Infect Dis 2000; 19: 112-7
27. Hummers-Pradier EVA, Koch M, Ohse AM, et al. Antibiotic resistance of urinary pathogens in female general practice patients. Scand J Infect Dis 2005; 37 (4): 256-61
28. Ungheri D, Albini E, Belluco G. In-vitro susceptibility of quinolone-resistant clinical isolates of *Escherichia coli* to fosfomycin trometamol. J Chemother 2002 Jun; 14 (3): 237-40
29. Marchese A, Gualco L, Debbia EA, et al. In vitro activity of fosfomycin against gram-negative urinary pathogens and the biological cost of fosfomycin resistance. Int J Antimicrob Agents 2003 Oct; 22 Suppl. 2: 53-9
30. Tempera G, Mirabile M, Mangiafico A, et al. Fosfomycin trimethamine in uncomplicated urinary tract infections: an epidemiological survey. J Chemother 2004 Apr; 16 (2): 216-7
31. Gesu GP, Marchetti F. Increasing resistance according to patient's age and sex in *Escherichia coli* isolated from urine in Italy. J Chemother 2007 Apr; 19 (2): 161-5
32. Sociedad Espanola de Enfermedades Infecciosas y Microbiologia Clinica (SEMIC). Protocolos clinicos 2003: infeccion urinaria [online]. Available from URL: http://www.semic.org/protocolos/clinicos/index.htm [Accessed 2007 Nov 12]
33. Hryniewicz K, Szczypa K, Sulikowska A, et al. Antibiotic susceptibility of bacterial strains isolated from urinary tract infections in Poland. J Antimicrob Chemother 2001 Jun; 47 (6): 773-80
34. Zemkova M, Kotlarova J, Merka V, et al. Emergence of fluoroquinolone resistance in *Escherichia coli* isolates at the department of clinical hematology. New Microbiol 2007 Oct; 30 (4): 423-30
35. Gobernado M, Valdes L, Alos JI, et al. Quinolone resistance in female outpatient urinary tract isolates of *Escherichia coli*: age-related differences. Rev Esp Quimio 2007; 20: 206-10
36. Gobernado M, Valdes L, Alos JI, et al. Antimicrobial susceptibility of clinical *Escherichia coli* isolates from uncomplicated cystitis in women over a 1-year period in Spain. Rev Esp Quimio 2007; 20: 68-76
37. Garcia MI, Munoz Bellido JL, Garcia Rodriguez JA, et al. In vitro susceptibility of community-acquired urinary tract pathogens to commonly used antimicrobial agents in Spain: a comparative multicenter study (2002-2004). J Chemother 2007 Jun; 19 (3): 263-70
38. Storby KA, Osterlund A, Kahlmeter G. Antimicrobial resistance in *Escherichia coli* in urine samples from children and adults: a 12 year analysis. Act Paed 2004 Apr; 93 (4): 487-91
39. Arslan H, Azap OK, Ergonul O, et al. Risk factors for ciprofloxacin resistance among *Escherichia coli* strains isolated from community-acquired urinary tract infections in Turkey. J Antimicrob Chemother 2005 Nov; 56 (5): 914-8
40. Rock W, Colodner R, Chazan B, et al. Ten years surveillance of antimicrobial susceptibility of community-acquired *Escherichia coli* and other uropathogens in Northern Israel (1995-2005). Isr Med Assoc J 2007 Nov; 9: 803-5
41. Hima-Lerible H, Menard D, Talarmin A. Antimicrobial resistance among uropathogens that cause community-acquired urinary tract infections in Bangui, Central African Republic. J Antimicrob Chemother 2003 Jan; 51 (1): 192-4
42. Randrianirina F, Soares JL, Carod JF, et al. Antimicrobial resistance among uropathogens that cause community-acquired urinary tract infections in Antananarivo, Madagascar. J Antimicrob Chemother 2007 Feb; 59 (2): 309-12
43. Issack MI, Yee Kin Tet HY, Morlat P. Antimicrobial resistance among enterobacteriaceae causing uncomplicated urinary tract infections in Mauritius: consequences of past misuse of antibiotics. J Chemother 2007 Apr; 19 (2): 222-5
44. Nabeth P, Perrier-Gros-Claude J-D, Juergens-Behr A, et al. In vitro susceptibility of quinolone-resistant Enterobacteriaceae

© 2008 Adis Data Information BV. All rights reserved.

uropathogens to fosfomycin trometamol, in Dakar, Senegal. Scand J Infect Dis 2005; 37 (6-7): 497-9
45. Dromigny JA, Nabeth P, Juergens-Behr A, et al. Risk factors for antibiotic-resistant *Escherichia coli* isolated from community-acquired urinary tract infections in Dakar, Senegal. J Antimicrob Chemother 2005 Jul; 56 (1): 236-9
46. Ahmed AA, Osman H, Mansour AM, et al. Antimicrobial agent resistance in bacterial isolates from patients with diarrhea and urinary tract infection in the Sudan. Am J Trop Med Hyg 2000; 63: 259-63
47. Akram M, Shahid M, Khan AU. Etiology and antibiotic resistance patterns of community-acquired urinary tract infections in JNMC Hospital Aligarh, India. Ann Clin Microbiol Antimicrob 2007; 6: 4
48. Arya SC, Agarwal N. Re: antibiotic resistance and trend of urinary pathogens in general outpatients from a major urban city. Int Braz J Urol 2007; 33: 267-9
49. Kahlmeter G. An international survey of the antimicrobial susceptibility of pathogens from uncomplicated urinary tract infections: the ECO.SENS Project. J Antimicrob Chemother 2003 Jan; 51 (1): 69-76
50. Urbanek K, Kolar M, Strojil J, et al. Utilization of fluoroquinolones and *Escherichia coli* resistance in urinary tract infection: inpatients and outpatients. Pharmacoepidemiol Drug Saf 2005 Oct; 14 (10): 741-5
51. Brown PD, Freeman A, Foxman B. Prevalence and predictors of trimethoprim/sulphamethoxazole resistance among uropathogenic *Escherichia coli* isolates in Michigan. Clin Infect Dis 2002 Apr 15; 34 (8): 1061-6
52. Wright SW, Wrenn KD, Haynes ML. Trimethoprim-sulfamethoxazole resistance among urinary coliform isolates. J Gen Intern Med 1999; 14: 606-9
53. McNulty CAM, Richards J, Livermore DM, et al. Clinical relevance of laboratory-reported antibiotic resistance in acute uncomplicated urinary tract infection in primary care. J Antimicrob Chemother 2006 Nov; 58 (5): 1000-8
54. Hillier S, Roberts Z, Dunstan F, et al. Prior antibiotics and risk of antibiotic-resistant community-acquired urinary tract infection: a case-control study. J Antimicrob Chemother 2007 Jul; 60 (1): 92-9
55. Gupta K, Stamm WE. Outcomes associated with trimethoprim/sulphamethoxazole (TMP/SMX) therapy in TMP/SMX resistant community-acquired UTI. Int J Antimicrob Agents 2002 Jun; 19 (6): 554-6
56. Metlay JP, Strom BL, Asch DA. Prior antimicrobial drug exposure: a risk factor for trimethoprim-sulfamethoxazole-resistant urinary tract infections. J Antimicrob Chemother 2003 Apr; 51 (4): 963-70
57. Kahan NR, Chinitz DP, Waitman DA, et al. Empiric treatment of uncomplicated urinary tract infection with fluoroquinolones in older women in Israel: another lost treatment option? Ann Pharmacother 2006 Dec; 40 (12): 2223-7
58. Blahna MT, Zalewski CA, Reuer J, et al. The role of horizontal gene transfer in the spread of trimethoprim-sulfamethoxazole resistance among uropathogenic Escherichia coli in Europe and Canada. J Antimicrob Chemother 2006 Apr; 57 (4): 666-72
59. Wright SW, Wrenn KD, Haynes M, et al. Prevalence and risk factors for multidrug resistant uropathogens in ED patients. Am J Emerg Med 2000 Mar; 18 (2): 143-6
60. Mentler PA, Kuhn BR, Gandhi G. Risk stratification for trimethoprim-sulfamethoxazole resistance in community-acquired, uncomplicated urinary tract infections. Am J Health-Syst Pharm 2006 Sep 1; 63 (17): 1588-90
61. Colodner R, Rock W, Chazan B, et al. Risk factors for the development of extended-spectrum beta-lactamase-producing bacteria in nonhospitalized patients. Eur J Clin Microbiol Infect Dis 2004 Mar; 23 (3): 163-7
62. Marijan T, Vranes J, Bedeni B, et al. Emergence of uropathogenic extended-spectrum beta lactamases-producing *Escherichia coli* strains in the community. Coll Antropol 2007; 31: 227-33
63. Goettsch WG, Janknegt R, Herings RM. Increased treatment failure after 3-day courses of nitrofurantoin and trimethoprim for urinary tract infections in women: a population-based retrospective cohort study using the PHARMO database. Br J Clin Pharmacol 2004 Aug; 58 (2): 184-9
64. Butler CC, Hillier S, Roberts Z, et al. Antibiotic-resistant infections in primary care are symptomatic for longer and increase workload: outcomes for patients with *E. coli* UTIs. Br J Gen Prac 2006 Sep; 56 (530): 686-92
65. Lawrenson RA, Logie JW. Antibiotic failure in the treatment of urinary tract infections in young women. J Antimicrob Chemother 2001 Dec; 48 (6): 895-901
66. Gupta K. Emerging antibiotic resistance in urinary tract pathogens. Infect Dis Clin North Am 2003 Jun; 17 (2): 243-59
67. Gross PA, Patel B. Reducing antibiotic overuse: a call for a national performance measure for not treating asymptomatic bacteriuria. Clin Infect Dis 2007 Nov 15; 45 (10): 1335-7
68. Hillier S, Bell J, Heginbothom M, et al. When do general practitioners request urine specimens for microbiology analysis? The applicability of antibiotic resistance surveillance based on routinely collected data. J Antimicrob Chemother 2006 Dec; 58 (6): 1303-6
69. Galatti L, Sessa A, Mazzaglia G, et al. Antibiotic prescribing for acute and recurrent cystitis in primary care: a 4 year descriptive study. J Antimicrob Chemother 2006 Mar; 57 (3): 551-6
70. Huang ES, Stafford RS. National patterns in the treatment of urinary tract infections in women by ambulatory care physicians. Arch Int Med 2002 Jan 14; 162 (1): 41-7
71. Kallen AJ, Welch HG, Sirovich BE. Current antibiotic therapy for isolated urinary tract infections in women. Arch Int Med 2006 Mar 27; 166 (6): 635-9
72. Wigton RS, Longenecker JC, Bryan TJ, et al. Variation by specialty in the treatment of urinary tract infection in women. J Gen Int Med 1999 Aug; 14 (8): 491-4
73. Lautenbach E, Larosa LA, Kasbekar N, et al. Fluoroquinolone utilization in the emergency departments of academic medical centers: prevalence of, and risk factors for, inappropriate use. Arch Int Med 2003 Mar 10; 163 (5): 601-5
74. Iravani A, Tice AD, McCarty J, et al. Short-course ciprofloxacin treatment of acute uncomplicated urinary tract infection in women: the minimum effective dose. Arch Intern Med 1995 Mar 13; 155 (5): 485-94
75. Vogel T, Verreault R, Gourdeau M, et al. Optimal duration of antibiotic therapy for uncomplicated urinary tract infection in older women: a double-blind randomized controlled trial. CMAJ 2004 Feb 17; 170 (4): 469-73
76. Arredondo-Garcia JL, Figueroa-Damian R, Rosas A, et al. Comparison of short-term treatment regimen of ciprofloxacin versus long-term treatment regimens of trimethoprim/sulfamethoxazole or norfloxacin for uncomplicated lower urinary tract infections: a randomized, multicentre, open-label, prospective study. J Antimicrob Chemother 2004 Oct; 54 (4): 840-3
77. Hooten TM, Scholes D, Gupta K, et al. Amoxicillin-clavulanate vs ciprofloxacin for the treatment of uncomplicated cystitis in women. a randomized trial. JAMA 2005 Feb 23; 293 (8): 949-55
78. Richard GA, Mathew CP, Kirstein JM, et al. 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 Mar; 59 (3): 334-9
79. Iravani A, Klimberg I, Briefer C, et al. A trial comparing low-dose, short-course ciprofloxacin and standard 7 day therapy

© 2008 Adis Data Information BV. All rights reserved.

with co-trimoxazole or nitroflurantoin in the treatment of uncomplicated urinary tract infections. J Antimicrob Chemother 1999; 43 Suppl. A: 67-75

80. McCarty JM, Richard G, Huck W, et al. A randomized trial of short-course ciprofloxacin, ofloxacin, or trimethoprim/sulfamethoxazole for the treatment of acute urinary tract infection in women. Am J Med 1999 Mar; 106 (3): 292-9
81. Schaeffer AJ, Stuppy BA. Efficacy and safety of self-start therapy in women with recurrent urinary tract infections. J Urol 1999 Jan; 161 (1): 207-11
82. Henry Jr 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 Dec; 24 (12): 2088-104
83. Fourcroy JL, Berner B, Chiang YK, et al. Efficacy and safety of a novel once-daily extended-release ciprofloxacin tablet formulation for treatment of uncomplicated urinary tract infection in women. Antimicrob Agents Chemother 2005 Oct; 49 (10): 4137-43
84. Bonfiglio G, Mattina R, Lanzafame A, et al. Fosfomycin tromethamine in uncomplicated urinary tract infections: a clinical study. Chemotherapy 2005 May; 51 (2-3): 162-6
85. Lobel B. Short term therapy for uncomplicated urinary tract infection today: clinical outcome upholds the theories. Int J Antimicrob Agents 2003 Oct; 22 Suppl. 2: 85-7
86. Gupta K, Hooton TM, Stamm WE. Isolation of fluoroquinolone-resistant rectal *Escherichia coli* after treatment of acute uncomplicated cystitis. J Antimicrob Chemother 2005 Jul; 56 (1): 243-6
87. 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: 1864-72
88. Minassian MA, Lewis DA, Chattopadhyay D, et al. A comparison between single-dose fosfomycin trametamol (Monuril®) and a 5-day course of trimethoprim in the treatment of uncomplicated lower urinary tract infection. Int J Antimicrob Agents 1998; 10: 39-47
89. Raz R, Chazan B, Kennes Y, et al. Empirical use of trimethoprim/sulphamethoxazole (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 May 1; 34 (9): 1165-9
90. Christiaens TC, DeMeyere M, Verschraegen G, et al. Randomised controlled trial of nitrofurantoin versus placebo in the treatment of uncomplicated urinary tract infection in adult women. Br J Gen Prac 2002 Sep; 52 (482): 729-34
91. Nicolle LE, Madsen KS, Debeeck GO, et al. Three days of pivmecillinam or norfloxacin for treatment of acute uncomplicated urinary infection in women. Scand J Infect Dis 2002; 34 (7): 487-92
92. Hooton TM, Winter C, Tiu F, et al. Randomized comparative trial and cost analysis of 3-day antimicrobial regimens for treatment of acute cystitis in women. JAMA 1995 Jan 4; 273 (1): 41-5
93. Masterton RG, Bochsler JA. High-dose co-amoxiclav in a single dose versus 7 days of co-trimoxazole as treatment of uncomplicated lower urinary tract infection in women. J Antimicrob Chemother 1995 Jan; 35 (1): 129-37
94. Leigh AP, Nemeth MA, Keyserling CH, et al. Cefdinir versus cefaclor in the treatment of uncomplicated urinary tract infection. Clin Ther 2000; 22: 818-25
95. Nicolle LE, Hoepelman AIM, Floor M, et al. Comparison of three days' therapy with cefcanel or amoxicillin for the treatment of acute uncomplicated urinary tract infection. Scand J Infect Dis 1993; 25 (5): 631-7
96. Gupta K, Hooten TM, Roberts PL, et al. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. Arch Intern Med 2007 Nov 12; 167 (20): 2207-12
97. O'Connor KA, Kingston M, Twomey C, et al. A trial comparing standard trimethoprim therapy with nitrofurantoin in the treatment of uncomplicated urinary tract infections in elderly patients [abstract]. Age Ageing 2002 Feb; 31 Suppl. 1: 13
98. Talan DA, Stamm WE, Hooten TM, et al. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis in women. a randomized trial. JAMA 2000 Mar 22/29; 283(12): 1583-90
99. Rubin RH, Shapiro ED, Andriole VT, et al. Evaluation of new anti-infective drugs for the treatment of urinary tract infection. Clin Infect Dis 1992 Nov; 15 Suppl. 1: S216-27
100. DeAlleaume L, Tweed EM. When are empiric antibiotics appropriate for urinary tract infection symptoms? J Fam Prac 2006 Apr; 55 (4): 338, 341-2
101. Kahan NR, Friedman NL, Lomnicky Y, et al. Physician specialty and adherence to guidelines for the treatment of unsubstantiated uncomplicated urinary tract infection among women. Pharmacoepidemiol Drug Saf 2005 May; 14 (5): 357-61
102. Barry HC, Ebell MH, Hickner J. Evaluation of suspected urinary tract infection in ambulatory women: a cost-utility analysis of office-based strategies. J Fam Prac 1997; 44: 49-60
103. Richards D, Toop L, Chambers S, et al. Response to antibiotics of women with symptoms of urinary tract infection but negative dipstick urine test results: a double-blind randomized controlled trial. BMJ 2005 Jul 16; 331 (7509): 143
104. Ejrnaes K, Sandvang D, Lundgren B, et al. Pulsed-field gel electrophoresis typing of *Escherichia coli* strains from samples collected before and after pivmecillinam or placebo treatment of uncomplicated community-acquired urinary tract infection in women. J Clin Microbiol 2006 May; 44 (5): 1776-81
105. Rosen DA, Hooten TM, Stamm WE, et al. Detection of intracellular bacterial communities in human urinary tract infections. PLOS Med 2007 Dec; 4 (12): 1949-58
106. Ottiger C, Schaer G, Huber AR. Time-course of quantitative urinary leukocytes and bacteria counts during antibiotic therapy in women with symptoms of urinary tract infection. Clin Chim Acta 2007 Apr; 379 (1-2): 36-41
107. Vinson DR, Quesenberry Jr CP. The safety of telephone management of presumed cystitis in women. Arch Intern Med 2004 May 10; 164 (9): 1026-9
108. Barry HC, Hickner J, Ebell MH, et al. A randomized controlled trial of telephone management of suspected urinary tract infections in women. J Fam Prac 2001 Jul; 50 (7): 589-94
109. Saint S, Scholes D, Fihn SD, et al. The effectiveness of a clinical practice guideline for the management of presumed uncomplicated urinary tract infection in women. Am J Med 1999 Jun; 106 (6): 636-41
110. Aagaard EM, Nadler P, Adler J, et al. An interactive computer kiosk module for the treatment of recurrent uncomplicated cystitis in women. J Gen Int Med 2006 Nov; 21 (11): 1156-9
111. Schauberger CW, Merkitch KW, Prell AM. Acute cystitis in women: experience with a telephone-based algorithm. Wisc Med J 2007; 106 (6): 326-9
112. McIsaac WJ, Moineddin R, Ross S. Validation of a decision aid to assist physicians in reducing unnecessary antibiotic drug use for acute cystitis. Arch Intern Med 2007 Nov 12; 167 (20): 2201-6
113. Gupta K, Hooten TM, Roberts PL, et al. Patient-initiated treatment of uncomplicated recurrent urinary tract infections in young women. Ann Intern Med 2001 Jul 3; 135 (1): 9-16
114. Lee BB, Simpson JM, Craig JC, et al. Methenamine hippurate for preventing urinary tract infections. Cochrane Database Syst Rev 2007; (4): CD003265

© 2008 Adis Data Information BV. All rights reserved.

115. Albert X, Huertas I, Pereiro II, et al. Antibiotics for preventing recurrent urinary tract infections in non-pregnant women. Cochrane Database Syst Rev 2004; (3): CD001209

116. Alexiou Z, Mouktaroudi M, Koratzanis G, et al. The significance of compliance for the success of antimicrobial prophylaxis in recurrent lower urinary tract infections: the Greek experience. Int J Antimicrob Ag 2007; 30: 40-3

117. Bauer HW, Alloussi S, Egger C, et al. A long-term, multicenter, double-blind study of an *Escherichia coli* extract (OM-89) in female patients with recurrent urinary tract infections. Eur Urol 2005; 47: 542-8

118. Darouiche RO, Thornby JI, Cerra-Stewart C, et al. Bacterial interference for prevention of urinary tract infection: a prospective, randomized, placebo-controlled, double-blind pilot trial. Clin Infect Dis 2005 Nov 15; 41 (10): 1531-4

119. Barrons R, Tassone D. Use of Lactobacillus probiotics for bacterial genitourinary infections in women: a review. Clin Ther 2008 Mar; 30 (3): 453-68

120. Reid G, Bruce AW. Probiotics to prevent urinary tract infections: the rationale and evidence. World J Urol 2006; 24: 28-32

121. McCully KS, Jackson S. Hormone replacement therapy and the bladder. J Br Menopause Soc 2004 Mar; 10 (1): 30-2

122. Rozenberg S, Pastijn A, Gevers R, et al. Estrogen therapy in older patients with recurrent urinary tract infections: a review. Int J Fertil Womens Med 2004 Mar-Apr; 49(2): 71-74

123. Andre M, Molstad S, Lundborg GS, et al. Management of urinary tract infections in primary care: a repeated 1-week diagnosis-prescribing study in five counties in Sweden in 2000 and 2002. Scand J Infect Dis 2004; 36 (2): 134-8

124. Martinez MA, Inglada L, Ochoa C, et al. Assessment of antibiotic prescription in acute urinary tract infections in adults. J Infect 2007; 54: 235-44

125. Warren JW, Abrutyn E, Hebel JR, et al. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis. Clin Infect Dis 1999 Oct; 29 (4): 745-58

126. Kahan E, Kahan NR, Chinitz DP. Urinary tract infection in women. Physician's preferences for treatment and adherence to guidelines: a national drug utilization study in a managed care setting. Eur J Clin Pharmacol 2003 Nov; 59 (8-9): 663-8

127. Grover ML, Bracamonte JD, Kanodia AK, et al. Assessing adherence to evidence-based guidelines for the diagnosis and management of uncomplicated urinary tract infection. Mayo Clin Proc 2007 Feb; 82 (2): 181-5

128. O'Connor PJ, Solberg LI, Christianson J, et al. 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: 673-82

129. Taur Y, Smith MA. Adherence to the Infectious Diseases Society of America guidelines in the treatment of uncomplicated urinary tract infection. Clin Infect Dis 2007 Mar 15; 44 (6): 769-74

130. Kahan NR, Chinitz DP, Waitman DA, et al. Empiric treatment of uncomplicated UTI in women: wasting money when more is not better. J Clin Pharm Ther 2004 Oct; 29 (5): 437-41

131. Kahan NR, Chinitz DP, Kahan E. Longer than recommended empiric antibiotic treatment of urinary tract infection in women: an avoidable waste of money. J Clin Pharm Ther 2004 Feb; 29 (1): 59-63

132. Kahan NR, Chinitz DP, Kahan E. Physician adherence to recommendations for duration of empiric antibiotic treatment for uncomplicated urinary tract infection in women: a national drug utilization analysis. Pharmacoepidemiol Drug Saf 2004 Apr; 13 (4): 239-42

133. Le TP, Miller LG. Empirical therapy for uncomplicated urinary tract infections in an era of increasing antimicrobial resistance: a decision and cost analysis. Clin Infect Dis 2001 Sep 1; 33 (5): 615-21

134. Berger RE. Duration of antibacterial treatment for uncomplicated urinary tract infection in women. J Urology 2006 Mar; 175 (3): 968

135. Nickel JC. Management of urinary tract infections: historical perspective and current strategies: part 2, modern management. J Urology 2005 Jan; 173 (1): 27-32

136. Gentry LO. Cephalosporins in urinary tract infection. Drugs 1987; 34 Suppl. 2: 154-63

137. Miller LG, Mehrotra R, Tang AW. Does in vitro fluoroquinolone resistance predict clinical failure in urinary tract infections? Int J Antimicrob Agents 2007; 29: 605-7

138. Stamey TA, Fair WR, Timothy MM, et al. Serum versus urinary antimicrobial concentrations in the cure of urinary-tract infections N Engl J Med 1974 Nov 28; 291(22): 1159-1163

139. Kaiser J, McPherson V, Kaufmann L. Which UTI therapies are safe and effective during breastfeeding? J Fam Prac 2007 Mar; 56 (3): 225-6, 228

140. Johnson JR, Owens K, Gajewski A, et al. *Escherichia coli* colonization patterns among human household members and pets, with attention to acute urinary tract infection. J Infect Dis 2008 Jan 15; 197 (2): 218-24

141. Ong CL, Ulett GC, Mabbett AN, et al. Identification of type 3 fimbriae in uropathogenic *Escherichia coli* reveals a role in biofilm formation. J Bacteriol 2008 Feb; 190 (3): 1054-63

Correspondence: Dr *David R.P. Guay*, College of Pharmacy, University of Minnesota, Weaver-Densford Hall 7-148, 308 Harvard Street SE, Minneapolis, MN 55455, USA.
E-mail: guayx001@umn.edu

© 2008 Adis Data Information BV. All rights reserved.