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## **Acute uncomplicated cystitis: from surveillance data to a rationale for empirical treatment**

Ioannis Katsarolis, Garyphallia Poulakou, Sofia Athanasia, Jenny Kourea-Kremastinou, Niki Lambri, Elias Karaiskos, Periklis Panagopoulos, Flora V. Kontopidou, Dionysios Voutsinas, Georgios Koratzanis, et al.

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## Acute uncomplicated cystitis: from surveillance data to a rationale for empirical treatment

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Livadia, Greece); Christos Kalyvas ('Hippocrates' Diagnostic Centre, Nikaia, Greece); and George Veliotis (Interamerican-Eurico, Athens, Greece).

## ABSTRACT

The objectives of this study were to explore the epidemiological features and resistance rates in uropathogens isolated from cases of acute uncomplicated cystitis (AUC) in Greece, and subsequently to guide empirical treatment. Urine samples from outpatients aged >16 years were cultured and for each uropathogen isolated non-susceptibility to orally administered antimicrobial agents was defined. Demographic and clinical data were provided in questionnaire form. From January 2005 to March 2006 a total of 1936 non-duplicate positive urinary cultures were collected and 889 AUC cases were evaluated. *Escherichia coli* was the main aetiological agent (83%). In the AUC group, non-susceptibility rates for *E. coli* isolates were as follows: amoxicillin 25.8%; co-trimoxazole 19.2%; cefalothin 14.9%; nitrofurantoin 10.7%; amoxicillin/clavulanic acid 5.2%; nalidixic acid 6%; mecillinam 3.4%; ciprofloxacin 2.2%; cefuroxime 1.7%, and fosfomycin 1.6%. Amoxicillin and/or co-trimoxazole use in the previous 3 months was significantly associated with isolation of a co-trimoxazole-resistant *E. coli* isolate. The same applied for previous use of a fluoroquinolone agent and isolation of a ciprofloxacin-resistant *E. coli* isolate. In conclusion, increased co-trimoxazole non-susceptibility rates undermine its use as a first-line agent in empirical treatment, especially in cases of recent use of co-trimoxazole and/or amoxicillin. Fluoroquinolones display potent in vitro activity against community uropathogens, but prudent use is warranted for uncomplicated infections. Mecillinam and nitrofurantoin could serve as effective front-line agents in an effort to design fluoroquinolones-sparing regimens.

## 1. Introduction

Acute uncomplicated cystitis (AUC) constitutes the real burden of urinary tract infections (UTIs) in the primary care setting and is usually treated empirically. The rationale for this approach is the predictable spectrum of uropathogens (*Escherichia coli* in 70–80% of cases) and the characteristic and distressing nature of the symptoms [1]. The choice of antimicrobial agent should be based on the in vitro susceptibility profiles of uropathogens in the geographic region of the practitioner, which are usually derived from laboratory-based surveillance systems. Ideally, for surveillance purposes physicians should send a urine sample from all patients with a clinical diagnosis of UTI. However, such a practice is not warranted by current guidelines [2]. Instead, a urine specimen is more likely to originate from a patient with a difficult-to-treat or recurrent infection or from patients with a complicated UTI, thus resulting in an overestimation of resistance rates among uropathogens in the community [3].

In the present study conducted in the Greek community, consecutive positive urine cultures were collected along with a questionnaire per culture, allowing classification (uncomplicated vs. complicated; cystitis vs. other types of UTI) and recording previous exposure to antibiotics. The present study represents a large-scale, multicentre surveillance study that was designed for the first time in Greece to explore epidemiology and resistance rates in AUC as well as to provide guidance on its empirical antibiotic treatment.

## 2. Materials and methods

A multicentre surveillance network was formed by private and public microbiology laboratories for outpatients in Attica region (Athens, Piraeus and suburbs), Thessaloniki (Northern Greece), Peloponnese (Southwestern Greece—Patras, Tripoli and Argolis) and Sterea Ellada (Central Greece—Karpenisi and Nafpaktos). Isolated strains were shipped to the central laboratory (Research Laboratory of Infectious Diseases and Antimicrobial Chemotherapy, 4th Department of Internal Medicine, Athens University School of Medicine, University General Hospital ATTIKON, Athens, Greece).

All outpatients not living in nursing health care or long-term residence facilities, older than 16 years of age and referred for a urine sample culture to each collaborating centre were asked to provide demographic and clinical information in a questionnaire (Fig. 1). A midstream urine culture was considered positive with growth of a single microorganism of  $>10^4$  colony-forming units/mL. Only one urine culture per patient was accepted in the study. A questionnaire structured to track clinical and epidemiological parameters for the evaluation of each sample was completed by the patients. Demographic data included gender, age and residence. Clinical data included reason for giving a urine sample, symptoms (fever, frequency, dysuria, haematuria, suprapubic pain, vaginal irritation or discharge), history of UTI (in the last 2 weeks, 3 months or previous year prior to sampling), recent use of antibiotics (in the previous 2 weeks or 3 months), history of hospital admission, insertion of a urinary catheter during the previous year, presence



of diabetes mellitus and nephrolithiasis, active presence of a urinary catheter and pregnancy on sampling.

### 2.1. Bacterial identification and antimicrobial susceptibility testing

Bacterial isolates were identified by biochemical profiling using API systems (bioMérieux, Basingstoke, UK). Antimicrobial susceptibility testing was performed using the disk diffusion method according to Clinical and Laboratory Standards Institute (CLSI) recommendations [4]. *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 29213, *Pseudomonas aeruginosa* ATCC 27853 and *Enterococcus faecalis* ATCC 29212 were used as quality control strains. Interpretative criteria for each antimicrobial tested were those recommended by the CLSI for non-susceptibility (i.e. intermediate-resistant and resistant strains). Antimicrobials tested were agents that can be administered orally: ampicillin (10 µg); amoxicillin/clavulanic acid (20/10 µg); cefalothin (30 µg); cefuroxime (30 µg); co-trimoxazole (1.25/23.75 µg); nitrofurantoin (300 µg); mecillinam (25 µg); fosfomycin (200 µg); nalidixic acid (30 µg); and ciprofloxacin (5 µg) (Oxoid Ltd., Cambridge, UK).

Ciprofloxacin minimum inhibitory concentrations (MICs) were determined by Etest (AB BIODISK, Solna, Sweden) in accordance with the manufacturer's instructions. CLSI breakpoints were used for analysis (susceptible  $\leq 1$  mg/L; resistant  $\geq 4$  mg/L) [4]. For each isolate, a quinolone-resistant phenotype was applied based on disk diffusion results as follows: nalidixic acid-

susceptible/ciprofloxacin-susceptible; nalidixic acid-resistant/ciprofloxacin-susceptible; and nalidixic acid-resistant/ciprofloxacin-resistant.

Microbiological analysis in the central laboratory was undertaken only for study purposes with no interference with the therapeutic decisions for each patient.

## 2.2. Definitions

Male gender, pregnancy, history of UTI in the last 2 weeks, history of admission to hospital in the last 30 days, presence of diabetes mellitus or nephrolithiasis, and the presence of a urinary catheter on sampling were considered as complicating factors.

Female patients without complicating factors presenting with at least one urinary symptom (i.e. frequency, dysuria, haematuria, suprapubic pain, excluding fever and vaginal symptoms) and a positive urine culture were assigned to the group 'acute uncomplicated cystitis' (AUC) [5].

## 2.3. Statistical analysis

A two-sided  $\chi^2$  test was used to test differences in resistance among groups.

Potential risk factors for isolation of *E. coli* vs. non-*E. coli* and for non-susceptibility of *E. coli* strains to co-trimoxazole and ciprofloxacin were processed by univariate analysis (i.e. gender, age, time and region of sampling, history of UTI, antibiotic use and presence of complicating factors).

Parameters with a *P*-value of <0.1 were entered for analysis in a multivariate logistic regression stepwise model. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. A *P*-value of ≤0.05 was considered statistically significant.

### 3. Results

#### 3.1. Demographics

During the surveillance period (1 January 2005 to 1 March 2006) a total of 1936 non-duplicate positive urinary cultures were collected. Of those, 1648 (85.1%) were from female patients, with a mean ± standard deviation age of 48.5 ± 18.9 years. From the original sample, 889 cases of AUC were evaluated (53.9% of the original female population). In complicated cases 45.5% of patients were male. Demographic and clinical data per group of patients are presented in Table 1.

#### 3.2. Distribution of species per type of infection, age and gender

*Escherichia coli* was the main aetiological agent (83% of the total yield). Non-*E. coli* uropathogens were more frequently isolated from patients aged >65 years (26%) compared with patients aged ≤65 years (14.3%) (*P* < 0.001; OR = 1.15, 95% CI 1.09–1.22) and from male patients (25%) compared with female patients (15.7%) (*P* < 0.001; OR = 1.79, 95% CI 1.33–2.41). Isolation rates for *E. coli* and non-*E. coli* species are depicted in detail for the different groups in Table 2. In the AUC group, isolation of a non-*E. coli* strain was not

significantly associated with age >65 years (20.2% for patients >65 years vs. 13.8% for patients ≤65 years;  $P = 0.074$ ).

For patients with a history of admission to hospital in the previous year, the likelihood of *E. coli* isolation decreased from 85.2% to 68.7% ( $P < 0.001$ ; OR = 0.38, 95% CI 0.28–0.51) as well as for those who had a urinary catheter inserted during the last year (from 83.8% to 67.3%;  $P < 0.001$ ; OR = 0.39, 95% CI 0.25–0.60).

### *3.3. Resistance rates for Escherichia coli per type of infection*

Non-susceptibility rates for *E. coli* isolates are listed per type of infection in Table 3. In the AUC isolates, amoxicillin showed the highest non-susceptibility rate (25.8%), followed by co-trimoxazole (19.2%), cefalothin (14.9%) and nitrofurantoin (10.7%). Non-susceptibility rates differed significantly between AUC and complicated cases, except for co-trimoxazole, mecillinam and fosfomycin.

### *3.4. Resistance rates for other uropathogens*

*Proteus* spp. (144 strains; 7.4% of total yield) and *Klebsiella* spp. (69 strains; 3.6% of total yield) formed the majority of non-*E. coli* species of the total study yield. Respective non-susceptibility rates for *Proteus* spp. and *Klebsiella* spp. isolates are provided in Table 4.

### 3.5. Fluoroquinolone in vitro activity against *Escherichia coli* isolates

Ciprofloxacin displayed statistically significant differences in non-susceptibility rates between complicated UTIs and AUC (7.9% vs. 2.2%, respectively;  $P < 0.001$ ). The same applied for nalidixic acid (12.7% vs. 6%, respectively;  $P < 0.001$ ). For 456 (60.3%) of the 756 *E. coli* strains isolated in the AUC group, ciprofloxacin MIC values were available. MIC<sub>50</sub>/MIC<sub>90</sub> values (MICs for 50% and 90% of the organism, respectively) for ciprofloxacin were 0.012 mg/L and 0.023 mg/L, respectively.

*Escherichia coli* strains from AUC cases are presented per phenotype of quinolone susceptibility with respect to ciprofloxacin MICs in Table 5. Eighteen strains (3.9%) susceptible to ciprofloxacin were resistant to nalidixic acid.

### 3.6. Risk factors for *Escherichia coli* resistance to co-trimoxazole and ciprofloxacin

In the univariate analysis, co-trimoxazole resistance was significantly associated with lack of suprapubic pain on presentation, history of at least three UTI episodes in the last year and use of amoxicillin or co-trimoxazole in the previous 3 months. In the multivariate analysis, only amoxicillin (OR = 3.610; 95% CI 1.510–8.620;  $P = 0.004$ ) or co-trimoxazole use (OR = 14.920; 95% CI 2.512–90.909;  $P = 0.003$ ) remained statistically significant.

For ciprofloxacin, only fluoroquinolone use in the previous 3 months was significantly associated with isolation of a ciprofloxacin-resistant *E. coli* strain (OR = 4.201, 95% CI 1.019–17.241;  $P = 0.047$ ).

## 4. Discussion

In the present study, use of a simple structured questionnaire helped to differentiate groups of patients comprising the spectrum of UTIs acquired and treated in the community. This approach allowed a more focused interpretation of laboratory-generated data regarding the susceptibility profile of uropathogens isolated in cases AUC [3,6]. Of note, 24% of isolated uropathogens from the total study yield originated from patients reporting lack of urinary symptoms. In this group of asymptomatic cases with significant bacteriuria (either with or without complicating features), the uropathogens isolated displayed significantly higher resistance rates than in the uncomplicated cystitis cases, which comprised ca. 46% of the total yield (data not shown). Evaluation of asymptomatic bacteriuria per se was out of the scope of the present study. *Escherichia coli* resistance rates for the antibiotics studied differed significantly between patients with and without the presence of complicating factors, with the exception of co-trimoxazole and mecillinam.

*Escherichia coli* remained the primary aetiological agent of UTIs (83% in total). Its isolation declined in cases of complicated infections. As shown by multivariate analysis, isolation of a non-*E. coli* isolate might warrant an investigation for the presence of putative complicating factors in certain cases [7]. *Staphylococcus saprophyticus* is infrequently isolated in Greek patients (<1% of lower UTIs). This finding confirms previous reports from Greece [8]. A possible bias of under-reporting the specific species is abated in the present

study as all positive urine cultures were sent to the central laboratory for further processing.

*Escherichia coli* resistance to co-trimoxazole plays a pivotal role in the empirical selection of therapeutic regimens for community-acquired uncomplicated UTIs [9]. Although resistance to co-trimoxazole in vitro does not automatically correlate with treatment failure [10], Infectious Diseases Society of America (IDSA) guidelines [9] advise against the use of co-trimoxazole as first-line treatment in areas where the prevalence of *E. coli* resistance to co-trimoxazole is >10–20%. Other studies support the use of co-trimoxazole even in a setting of 22% resistance rate [11]. In the present study, the prevalence of co-trimoxazole resistance in uncomplicated cystitis isolates was 19%. The only significant parameter affecting co-trimoxazole resistance in *E. coli* isolates was the use of amoxicillin and/or co-trimoxazole in the previous 3 months. Patients who had a course of these antibiotics in the previous 3 months carried a two-fold risk of having an infection with a co-trimoxazole-resistant isolate. The relationship between antibiotic prescribing and risk of harbouring a co-trimoxazole-resistant *E. coli* UTI isolate has also been documented by Hillier et al. [12] at an individual level.

Non-susceptibility rates for co-trimoxazole undermine its position as a first-line agent for the empirical treatment of uncomplicated cystitis in the Greek community. Nevertheless, the use of co-trimoxazole may still be advocated in cases of non-exposure to co-trimoxazole and/or amoxicillin in the recent past, bearing in mind that it has been reported that even with a 30% co-trimoxazole

resistance rate the bacteriological eradication rate is predicted to be 80% and the clinical cure rate 85% (when for 0% resistance, predicted rates are 93% and 95%, respectively) [13].

In the setting of increased co-trimoxazole resistance in the community, fluoroquinolones are recommended by scientific authorities as an alternative first-line choice in the empirical treatment of community-acquired UTIs [2]. Fluoroquinolones display excellent in vitro activity against most uropathogens and can be administered as a short duration regimen [14]. The low prevalence of ciprofloxacin resistance (5.1% in total; 2.2% in acute uncomplicated cystitis) is appealing and tempting for prescribing. Nevertheless, nalidixic acid in vitro activity can provide helpful hints for predicting the in vivo efficacy of fluoroquinolones in vivo [15]. Strains resistant to nalidixic acid have already acquired in the majority the first-step mutation for fluoroquinolone resistance, although still remaining susceptible to ciprofloxacin. Exposure to a fluoroquinolone can select in turn for strains fully resistant to fluoroquinolones. In our study population, ca. 4% of the *E. coli* population was nalidixic acid-resistant and ciprofloxacin-sensitive. In this population, the MICs for ciprofloxacin ranged between 0.047 mg/L and 1 mg/L (still considered susceptible according to CLSI breakpoints).

A more sceptical approach should be implemented for the empirical use of fluoroquinolones in the case of uncomplicated community infections such as cystitis. A shift towards indiscriminate prescription of fluoroquinolones in the community for cystitis could select for fluoroquinolone-resistant



microorganisms. As shown in the present study, the risk of carrying a ciprofloxacin-resistant strain was increased by seven-fold more if the patient had received a fluoroquinolone in the previous 3 months. In addition to the individual level [16], the association of increasing prescription rates of fluoroquinolones with increasing resistance rates to fluoroquinolones in the same areas has also been documented [17]. Johnson et al. [18] recently described the emergence of fluoroquinolone resistance in outpatient urinary *E. coli* isolates following an institutional policy change for the empirical treatment of UTI in Denver; in 1999, owing to increased co-trimoxazole resistance rates of 24%, a switch to levofloxacin as initial treatment of UTI was advised. By 2005, levofloxacin prescriptions quadrupled (from 3.1 to 12.7 prescriptions per 1000 outpatient visits) and levofloxacin resistance in *E. coli* rose from 1% to 9.4%. This rapid emergence of resistance forced authorities to switch their recommendations to fluoroquinolones-sparing regimens (such as nitrofurantoin).

In the context of designing a fluoroquinolone-sparing management approach, mecillinam stands as a potent first-line therapeutic agent in the Greek community. Mecillinam [19] displays low resistance rates in community-acquired uropathogens. It has been used for more than 20 years in the Nordic countries in AUC, where the sustained in vitro efficacy against Enterobacteriaceae despite widespread use and the low level of side effects still support its use. In the ARESC study [20], a multinational surveillance project in nine European countries and Brazil from 2003–2006, mecillinam also displayed an excellent susceptibility profile without any statistical

variability among different countries (maximum non-susceptibility rate 4%; mean 2.8%). As pivmecillinam (the prodrug of mecillinam) is a  $\beta$ -lactam, it is suitable for use in women at child-bearing age or in pregnant patients. The concern for its activity against *S. saprophyticus* is abated by the fact that it has been shown to provide comparable outcomes with other antibiotics against *S. saprophyticus* infections owing to its pharmacokinetic/pharmacodynamic properties. Moreover, *S. saprophyticus* does not pose a serious problem in the Greek community, as displayed by its isolation rates in this study (<1%) and in other studies such as ECO.SENS [8].

As far as the other available oral agents are concerned, nitrofurantoin can be used as a fluoroquinolones-sparing agent in patients with AUC [21]. The short course of 5–7 days precludes its known side effects with long-term use. It has a single indication for AUC (except for *Proteus* spp., which is intrinsically resistant) and a limited ecological effect on faecal flora, portending less pressure for antimicrobial resistance development. Its in vitro activity has been preserved internationally, as recently shown in other studies [20].

Amoxicillin is no longer a viable option for empirical use for community-acquired UTIs, as resistance rates rise to >25% in cases of uncomplicated infection. On the other hand,  $\beta$ -lactams [2] (such as amoxicillin/clavulanic acid, cefalexin and cefuroxime axetil) need to be prescribed for 7 days and the cure rates are suboptimal compared with non- $\beta$ -lactam agents.

Fosfomycin [2,20,22] could provide an efficient alternative choice given the fact that it has a good safety profile, excellent in vitro activity and a favourable once-daily dosing regimen. Nevertheless, it has not been marketed in Greece since the early 2000s.

## **5. Conclusion**

The choice of antibiotic in empirical treatment of AUC should result from a cautious balance between the available in vitro susceptibility data from the specific target population and the tolerability and ecological effects of the prescribed agent. For patients with AUC in Greece, increased co-trimoxazole resistance rates undermine its use as a first-line agent. Fluoroquinolones still display excellent in vitro activity against most uropathogens but the increasing resistance rates to nalidixic acid should prompt caution in their overuse for uncomplicated infections in the community. In Greece, mecillinam and nitrofurantoin could serve as effective frontline agents in an effort to design fluoroquinolones-sparing regimens.

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### **Competing interests**

None declared.

### **Ethical approval**

The research protocol was approved by the ethics committees of all co-operating hospitals.

## References

- [1] Nicolle LE. Uncomplicated urinary tract infection in adults including uncomplicated pyelonephritis. *Urol Clin North Am* 2008;35:1–12.
- [2] Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). *Clin Infect Dis* 1999;29:745–58.
- [3] Hillier S, Bell J, Heginbothom M, Roberts Z, Dunstan F, Howard A, 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;58:1303–6.
- [4] Clinical and Laboratory Standards Institute. *Performance standards for antimicrobial susceptibility testing*. Sixteenth informational supplement. Document M100-S16. Wayne, PA: CLSI; 2006.
- [5] Tice AD. Short-course therapy of acute cystitis: a brief review of therapeutic strategies. *J Antimicrob Chemother* 1999;43(Suppl A):85–93.
- [6] Ti TY, Kumarasinghe G, Taylor MB, Tan SL, Ee A, Chua C, et al. What is true community-acquired urinary tract infection? Comparison of pathogens identified in urine from routine outpatient specimens and from community clinics in a prospective study. *Eur J Clin Microbiol Infect Dis* 2003;22:242–5.
- [7] Ronald A. The etiology of urinary tract infection: traditional and emerging pathogens. *Am J Med* 2002;113(Suppl 1A):14S–9S.

- [8] Kahlmeter G; ECO.SENS. An international survey of the antimicrobial susceptibility of pathogens from uncomplicated urinary tract infections: the ECO.SENS Project. *J Antimicrob Chemother* 2003;51:69–76.
- [9] Hooton TM, Besser R, Foxman B, Fritsche TR, Nicolle LE. Acute uncomplicated cystitis in an era of increasing antibiotic resistance: a proposed approach to empirical therapy. *Clin Infect Dis* 2004;39:75–80.
- [10] Gupta K, Stamm WE. Outcomes associated with trimethoprim/sulphamethoxazole (TMP/SMX) therapy in TMP/SMX resistant community-acquired UTI. *Int J Antimicrob Agents* 2002;19:554–6.
- [11] Guay DR. Contemporary management of uncomplicated urinary tract infections. *Drugs* 2008;68:1169–205.
- [12] Hillier S, Roberts Z, Dunstan F, Butler C, Howard A, Palmer S. Prior antibiotics and risk of antibiotic-resistant community-acquired urinary tract infection: a case–control study. *J Antimicrob Chemother* 2007;60:92–9.
- [13] Gupta K. Addressing antibiotic resistance. *Am J Med* 2002;113(Suppl 1A):29S–34S.
- [14] Hooton TM. Fluoroquinolones and resistance in the treatment of uncomplicated urinary tract infection. *Int J Antimicrob Agents* 2003;22(Suppl 2):65–72.
- [15] Aubert G, Carricajo A, Fonsale N, Vautrin AC. Optimization of the use of ciprofloxacin. *Pathol Biol (Paris)* 2009;57:236–9.
- [16] Arslan H, Azap OK, Ergönül O, Timurkaynak F; Urinary Tract Infection Study Group. Risk factors for ciprofloxacin resistance among *Escherichia coli* strains isolated from community-acquired urinary tract infections in Turkey. *J Antimicrob Chemother* 2005;56:914–8.

- [17] Gobernado M, Valdés L, Alós JI, García-Rey C, Dal-Ré R, García-de-Lomas J; Spanish Surveillance Group for Urinary Pathogens. Antimicrobial susceptibility of clinical *Escherichia coli* isolates from uncomplicated cystitis in women over a 1-year period in Spain. *Rev Esp Quimioter* 2007;20:68–76.
- [18] Johnson L, Sabel A, Burman WJ, Everhart RM, Rome M, MacKenzie TD, et al. Emergence of fluoroquinolone resistance in outpatient urinary *Escherichia coli* isolates. *Am J Med* 2008;121:876–84.
- [19] Graninger W. Pivmecillinam—therapy of choice for lower urinary tract infection. *Int J Antimicrob Agents* 2003;22(Suppl 2):73–8.
- [20] Naber KG, Schito G, Botto B, Palou J, Mazzei T. Surveillance study in Europe and Brazil on clinical aspects and antimicrobial resistance epidemiology in females with cystitis (ARESC): implications for empiric therapy. *Eur Urol* 2008;54:1164–78.
- [21] Arya SC, Agarwal N. Nitrofurantoin: the return of an old friend in the wake of growing resistance. *BJU Int* 2009;103:994–5.
- [22] Gupta K, Hooton TM, Stamm WE. Increasing antimicrobial resistance and the management of uncomplicated community-acquired urinary tract infections. *Ann Intern Med* 2001;135:41–50.



**Fig. 1.** Study questionnaire.

**Table 1**

Demographics and clinical data per type of infection

	No. with AUC (%)	Total no. (%)
No. of patients (% of total)	889 (45.9)	1936 (100)
Gender (% female)	100	85.1
Age (mean ± S.D.) (range) (years)	44.5 ± 17.2 (16–97)	50.1 ± 18.9 (16–97)
Age group (years)		
15–65	734 (82.6)	1403 (72.5)
>65	124 (13.9)	454 (23.5)
Unknown	31 (3.5)	79 (4.1)
Region of sampling		
Athens	743 (83.6)	1608 (83.1)
Thessaloniki	68 (7.6)	168 (8.7)
Peloponnese	52 (5.8)	100 (5.2)
Sterea Ellada	26 (2.9)	60 (3.1)
Period of sampling		
Jan–Mar 2005	65 (7.3)	165 (8.5)
Apr–June 2005	341 (38.4)	782 (40.4)
July–Sept 2005	179 (20.1)	363 (18.8)
Oct–Dec 2005	161 (18.1)	306 (15.8)
Jan–Mar 2006	115 (12.9)	247 (12.8)
Data not available	28 (3.1)	73 (3.8)
Private/public laboratory	725/164 (81.6/18.4)	1476/460 (76.2/23.8)
Hospital/primary care laboratory	135/754 (15.2/84.8)	400/1536 (20.7/79.3)
History of previous UTI in the last 2 weeks	0 <sup>a</sup>	109 (5.6)
History of admission in the last year	56 (6.3)	259 (13.4)
History of urinary catheter placement during admission	29 (3.3)	104 (5.4)

Diabetes mellitus	0 <sup>a</sup>	216 (11.2)
Nephrolithiasis	0 <sup>a</sup>	203 (10.5)
Actively having a urinary catheter	0 <sup>a</sup>	85 (4.4)
Pregnancy	0 <sup>a</sup>	42 (2.2)
History of UTI in the last 3 months	101 (11.4)	322 (16.6)
History of UTI in the past	345 (38.8)	752 (38.8)
History of receiving antibiotic in the last 3 months for reason other than UTI	169 (19.0)	410 (21.2)

AUC, acute uncomplicated cystitis; S.D., standard deviation; UTI, urinary tract infection.

<sup>a</sup> Not applicable by protocol definition.

**Table 2**

Uropathogen distribution per type of infection, age group and gender

Uropathogen	Uropathogen distribution (%)						Total (%)
	Age		Gender		Type of infection		
	15–65 years	>65 years	Male	Female	AUC	Complicated UTI	
<i>Escherichia coli</i>	85.7	74.0	75.0	84.3	85.4 *	79.9 *	83.0
Non- <i>E. coli</i>	14.3 **	26.0 **	25.0 **	15.7 **	14.6	20.1	17.0
<i>Proteus</i> spp.	6.5	9.7	7.3	7.5	7.4	8.0	7.4
<i>Klebsiella</i> spp.	3.1	5.3	3.1	3.6	3.0	2.9	3.6
<i>Enterococcus</i> spp.	1.6	3.3	5.9	1.3	1.2	3.1	2.0
<i>Pseudomonas</i> spp.	0.9	4.0	6.3	0.8	0.3	3.1	1.7
<i>Staphylococcus</i> spp.	0.9	1.3	1.0	1.0	1.1	1.3	1.0
<i>Citrobacter</i> spp.	0.5	0.9	0.7	0.5	0.6	0.8	0.6
<i>Enterobacter</i> spp.	0.4	1.1	–	0.7	0.7	0.4	0.6
Other	0.3	0.4	0.7	0.2	0.2	0.4	0.3

AUC, acute uncomplicated cystitis; UTI, urinary tract infection.

\*  $P = 0.042$ ; \*\*  $P < 0.001$ .

**Table 3**

*Escherichia coli* non-susceptibility rates per type of infection

Antimicrobial agent	AUC	Complicated UTIs	Total	P-value (AUC vs. complicated UTIs)
Amoxicillin	25.8	33.1	29.6	0.005
Amoxicillin/clavulanic acid	5.2	7.1	6.6	0.009
Cefalothin	14.9	20.8	19.2	<0.001
Cefuroxime	1.7	3.9	3.3	<0.001
Co-trimoxazole	19.2	19.9	20	0.347
Nalidixic acid	6	12.7	9.5	<0.001
Ciprofloxacin	2.2	7.9	5.1	<0.001
Mecillinam	3.4	6.1	4.2	0.492
Nitrofurantoin	10.7	13.6	13	0.003
Fosfomycin	1.6	2.4	1.9	0.196

AUC, acute uncomplicated cystitis; UTI, urinary tract infection.

**Table 4**

Non-susceptibility rates in acute uncomplicated cystitis (AUC) cases and in the total study population for *Proteus* spp. and *Klebsiella* spp.

Antimicrobial agent	<i>Proteus</i> spp.		<i>Klebsiella</i> spp.	
	AUC ( <i>n</i> = 66)	Total ( <i>n</i> = 144)	AUC ( <i>n</i> = 27)	Total ( <i>n</i> = 69)
Amoxicillin	30.3	35.4	N/A	N/A
Amoxicillin/clavulanic acid	3	2.8	0	7.2
Cefalothin	10.6	14	7.4	14.5
Cefuroxime	0	2.8	0	5.8
Co-trimoxazole	21.2	23.2	7.4	17.4
Mecillinam	24.4	23.1	0	0
Fosfomicin	12.1	14.6	11.1	13
Nalidixic acid	13.6	12.6	0	13
Ciprofloxacin	3	2.1	0	8.7
Nitrofurantoin	N/A	N/A	40.7	40.6

N/A, not applicable.

**Table 5**

Ciprofloxacin (CIP) minimum inhibitory concentration (MIC) distribution of *Escherichia coli* isolates per fluoroquinolone resistance phenotype in patients with acute uncomplicated cystitis

CIP MIC (mg/L)	NAL <sup>r</sup> CIP <sup>r</sup>	NAL <sup>r</sup> CIP <sup>s</sup>	NAL <sup>s</sup> CIP <sup>s</sup>	Total
0.003			2	2
0.004			13	13
0.006			60	60
0.008			151	151
0.012			135	135
0.016			47	47
0.023			13	13
0.032			3	3
0.047		3		3
0.064			1	1
0.094			2	2
0.125		2	1	3
0.19		9		9
0.25		1		1
0.38		1		1
0.5		1	1	2
1		1		1
6				
8	1			1
12	1			1
32	7			7
Total (%)	9 (2.0)	18 (3.9)	429 (94.1)	456 (100)

NAL<sup>r</sup>CIP<sup>r</sup>, nalidixic acid-resistant/ciprofloxacin-resistant; NAL<sup>r</sup>CIP<sup>s</sup>, nalidixic acid-resistant/ciprofloxacin-susceptible; NAL<sup>s</sup>CIP<sup>s</sup>, nalidixic acid-susceptible/ciprofloxacin susceptible.

1. Date of sampling
2. Patient's initials
3. Sampling centre
4. Gender
5. Date of birth
6. Reason for urine culture
  - Fever
  - Frequency
  - Dysuria
  - Haematuria
  - Suprapubic pain
  - Previous urinary tract infection (UTI)
  - Vaginal irritation or discharge
  - Other, please specify
7. UTI in the last 2 weeks, yes or no? If yes, what antibiotic were you prescribed?
8. UTI in the last 3 months (last 2 weeks not included), yes or no? If yes, what antibiotic were you prescribed?
9. History of a UTI in the past (last 2 weeks or 3 months not included), yes or no?
10. Have you received antibiotics for any other reason in the last 3 months, yes or no? If yes, which antibiotic (provide name)
11. Have you been admitted in the hospital in the last year, yes or no? If yes, when? If yes, reason for admission? Did you have a urinary tract catheter, yes or no?
12. Do you suffer from:
  - Diabetes mellitus
  - Nephrolithiasis
13. Actively having a urinary tract catheter, yes or no? If yes, when was it placed?
14. (For women) Are you pregnant, yes or no?