ISSN 1124-9390

LE INFEZIONI IN MEDICINA

Position paper on uncomplicated cystitis and single dose antibiotic therapy with prulifloxacin

www.infezmed.it

Vol. 24 - Supplemento 1 - 2016

EDIMES
Edizioni Medico Scientifiche - Pavia

LE INFEZIONI IN MEDICINA

Rivista trimestrale di eziologia, epidemiologia, diagnostica, clinica e terapia delle patologie infettive

Volume 24 - Suppl. n. 1 - 2016

EDIZIONI INTERNAZIONALI srl
EDIMES
Edizioni Medico Scientifiche - Pavia

Edizioni Internazionali srl
Divisione EDIMES
Edizioni Medico-Scientifiche - Pavia

Via Riviera 39 - 27100 Pavia
Tel. 0382/526253
Fax 0382/423120
e-mail: edint.edimes@tin.it

Registrazione
Trib. di Milano n. 506
del 6/9/2007

Direzione e Redazione

Dipartimento di Medicina e Chirurgia
Università degli Studi di Salerno
Via Allende, Baronissi, Salerno - Italy
Tel. 0039 (089) 672420
e-mail: infezioniinmedicina@libero.it
www.infezmed.it

Direttore responsabile
P.E. Zoncada

SOMMARIO

LE INFEZIONI IN MEDICINA

A quarterly journal covering the etiological, epidemiological, diagnostic, clinical and therapeutic aspects of infectious diseases

Introduction

Silvano Esposito
Department of Infectious Diseases, University of Salerno, Italy

Urinary tract infection (UTI) is characterized by the presence of $>10^5$ microorganisms per milliliter of urine with pus cells and red blood cells [1]
The term uncomplicated urinary tract infection refers to the invasion of a structurally and functionally normal urinary tract by a nonresident infectious organism while complicated UTI refers to the occurrence of infection in patients with an abnormal structural or functional urinary tract, or both.
UTI is differentiated from asymptomatic bacterial colonization by the presence of an inflammatory response, and the associated signs and symptoms that result from bacterial invasion.
Acute uncomplicated bacterial cystitis is common in general practice and among sexually active young women, the incidence of symptomatic urinary tract infection (UTI) is high. Risk factors include recent sexual intercourse, recent spermicide use, and a history of urinary tract infection [2].
Most episodes of cystitis are generally considered to be uncomplicated in otherwise healthy non pregnant adult women as not associated with an underlying condition that increases the risk of infection or of failing therapy (such as obstruction, anatomic abnormality, urologic dysfunction, or a multiply-resistant uropathogen).
It has been estimated that at least one-third of all women in the United States are diagnosed with a UTI by the time they reach 24 years of age [3]. According to the National Health and Nutrition Examination Survey (NHANES-III), the incidence for UTI is 13,320 per 100,000 adult women per year. [4] Among young healthy women with cystitis, the infection recurs in 25% of women within 6 months after the first episode.
Women are especially susceptible to cystitis for reasons that are poorly understood. One factor may be that a woman's urethra is short, allowing bacteria quick access to the bladder. Also, a woman's urethral opening is near sources of bacteria from the anus and vagina.
Uncomplicated cystitis in the women are commonly caused by Gram negative organisms like Escherichia coli, Klebsiella, Proteus, Pseudomonas, Enterobacter and also less commonly by gram positive organisms like Staphylococcus saprophyticus [5]. Co-trimoxazole, β-lactams, aminoglycosides, and fluroquinolones are the groups of antimicrobials commonly prescribed for treatment of UTI [6].
Short duration treatment leads to better patient compliance, less adverse effects and cost reduction.
Acute uncomplicated bacterial cystitis are common in general practice and because of their high frequent occurrence they do represent a cause of particular concern. This supplement includes a position paper giving a multidisciplinary approach to the management of the same diseases that can be frequently observed in the everyday medical practice by different specialists (infectious diseases specialist , urologist, gynecologist).

REFERENCES

[1] Nicolle L.E. Epidemiology of urinary tract infections. *Clin. Microbiol. Newsl* 24, 135–140, 2002.
[2] Hooton T.M., Scholes D., Hughes J.P., et al. A prospective study of risk factors for symptomatic urinary tract infection in young women. *N. Engl. J. Med*. 335, 7, 468, 1996.
[3] Patton J.P., Nash D.B., Abrutyn E. Urinary tract infection: economic considerations. *Med. Clin. North Am.* 75, 495–513, 1991.
[4] Foxman B., Brown P. Epidemiology of urinary tract infections: transmission and risk factors, incidence, and costs. *Infect. Dis. Clin. North Am.* 17, 227-241, 2003.
[5] Lawrenson R.A., Logie J.W. Antibiotic failure in the treatment of urinary tract infections in young women. *J. Antimicrob. Chemother.* 48, 6, 895-901, 2001.
[6] Trienekens T.A.M., London N.H.HJ., Houben A.W. Double-blind comparison of 3-day versus 7-day treatment with norfloxacin in symptomatic urinary tract infections. The Inter-Nordic Urinary Tract Infection Study Group. *Scand. J. Infect. Dis.* 20, 6, 619-624, 1988.

Position paper on uncomplicated cystitis and single dose antibiotic therapy with prulifloxacin

Carlo Tascini[1], Rossella Nappi[2], Luigi Cormio[3], Massimo Lazzeri[4], Gabriele Alberto Saracino[5], Chiara Benedetto[6]

[1]U.O. Infectious Diseases, Nuovo Santa Chiara Hospital, Pisa, Italy;
[2]Research Center for Reproductive Medicine, Gynecological Endocrinology and Menopause, IRCCS S. Matteo Foundation, Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Italy;
[3]Department of Urology and Renal Transplantation, University of Foggia, Italy;
[4]Department of Urology, Istituto Clinico Humanitas IRCCS, Clinical and Research Hospital, Rozzano, Milan, Italy;
[5]UOC Urology I, bari University, Policlinico di Bari, Italy;
[6]Obstetrics & Gynaecology I, Department of Surgical Sciences, University of Torino, Italy

SUMMARY

Episodes of acute cystitis occurring occasionally in healthy pre-menopausal, non-pregnant women, with no history suggestive of an abnormal urinary tract, are generally classified as uncomplicated cystitis.

Uncomplicated cystitis (UC) is diagnosed by the clinical point of view according to the following symptoms: patients with dysuria, pollakiuria, stranguria, without fever and without flank pain. UC with blood in the urine is possible. Blood is not a criterion used to classify an UTIs as complicated.

Urine cultures and/or dip stick results are not necessary for the diagnosis of UC. The most frequent pathogen of UC is E. coli, followed by S. saprophyticus and other enterobacteria. In UC MDR microrganisms are rare. Fluoroquinolones are the most frequently used drugs, followed by fosfomycin, cotrimoxazole and nitrofurantoin.

For many investigators traditional dosage regimes for UC are eccessive. Ideally a patient should be treated with the shortest course of the safest and less expensive drug that will eradicate the offending organism.

Many women with cystitis will stop their prescribed treatment when their symptoms are resolved. This is often after the first few doses and explains why these women often have a supply of antimicrobial agents available at home.

Therefore a single dose antibiotic therapy for UC may be useful in order to reduce the antibiotic pressure and to reduce the prescription of diagnostic examinations. A woman who is treated successfully with single dose therapy is unlikely to have a urinary tract abnormality. The practical consequence of this is that only those women who are single-dose failures warrant urinary tract investigation. Furthermore, a single dose of an antimicrobial drug is associated with fewer side effects.

Among drugs used to treat UC, single dose fluoroquilones was as effective as other drugs used in single dose. Prulifloxacin was approved in Italy for single dose therapy for UC. Prulifloxacin efficacy in UC may be due, beside its broad-spectrum antimicrobial activity, to its long post-antibiotic effect.

Prulifloxacin, in single dose, may have less adverse effect than prolonged treatment and this is also true with other fluoroquinolones. Furthermore, due to lack of activity towards anaerobes, prulifloxacin may respect the fecal microbioma and reduce the risk of C. difficile colitis.

In conclusion UC might be treated with a single dose of a potent fluoroquinolone such as prulifloxacin.

INTRODUCTION

Definition and clinical diagnosis

Uncomplicated cystitis (UC): Episodes of acute cystitis occurring occasionally in healthy pre-menopausal, non-pregnant women, with no history suggestive of an abnormal urinary tract, renal insufficiency or co-morbidities, are generally classified as uncomplicated, whereas all others are classified as complicated (simple cystitis might be a synonymous with uncomplicated cystitis). Because definition of UC is not clear to the different physicians who care for it; including general practitioners, gynecologists, urologists and infectious disease specialists,

Indirizzo per la corrispondenza
Carlo Tascini
e-mail: c.tascini@ao-pisa.toscana.it

a survey was performed by a marketing agency. A survey performed in Italy on general practitioners (GP) (160) and gynecology specialists (Gy) (80) about uncomplicated cystitis (UC) has given different results about diagnosis, antibiotic treatment and length of treatment. Many physicians (25% of GP and 33% of Gy) believe that urinalysis and/or urine culture, differently from guidelines, are necessary for the diagnosis of UC.
Only 15% of the participating doctors believe that sporadic cystitis is an UC; in fact recurrence (caused by the same microorganism) or relapsing cystitis (caused by a different microorganism) is complicated cystitis (at least three episodes in one year or at least two episodes in the last 6 months). For 15% of GP and 8% of Gy, hematuria excludes UC. Instead from the definition of UC, this condition may have hematuria. Absence of fever is a major criteria for defining UC: only 12% of GP and 7% of Gy, correctly define UC based on the absence of fever. Although many physicians believe that drugs to treat UC have to be effective, rapidly bactericidal, have few adverse effects and easily accepted by patients. Only 5% of GP and 3% of Gy know that a single dose of antibiotic might be effective in the treatment of UC [Mencacci F, Personal comunication].
In order to better define the possibility of treating UC with a single dose of antibiotic, a consensus among 6 Italian experts (1 ID C.T, 2 Gy, R.N, C. B, 3 urologists, L. C., M. L., A. S.) was agreed to write a position paper on definition, diagnosis and single dose treatment of UC.
From a management point of view it has been found extremely valuable to consider UTI as uncomplicated or complicated:

Uncomplicated
- normal urinary tract,
- normal renal function,
- no co-morbidities,
- no pregnancy,
- no menopause.

Complicated
- abnormal urinary tract: bladder-urethra stones, vesico-ureteric reflux, obstruction, paraplegia, atonic bladder, indwelling catheter, chronic prostatitis;
- Impaired host defense such as neutropenia, diabetes mellitus, immune-suppressive therapy;
- Impaired renal function;
- Virulent microrganisms: urease-producing *Proteus* spp, metastatic staphylococcal infections;
- All males [1].

Uncomplicated cystitis is diagnosed from the clinical point of view; patient with dysuria, pollakiuria, stranguria. UC with blood in urine is possible. Blood is not a criterion used to classify UTIs as complicated. Instead clinical manifestations suggestive of pyelonephritis include fever (temperature >37,5°C), chills, flank pain, costo-vertebral-angle tenderness, and nausea or vomiting. Dysuria is also common with urethritis or vaginitis, but cystitis is more likely when symptoms include frequency, urgency, or hematuria, when the onset of symptoms is sudden or severe, and when vaginal irritation and discharge are not present [2, 3].
Acute UC is a benign condition, with frequent early resolution of symptoms and only rare cases of progression to pyelonephritis [1]. However, cystitis is associated with considerable morbidity, and antimicrobial drugs are routinely prescribed in order to reach a rapid resolution of symptoms [1]. The choice of therapy has become more difficult as antimicrobial resistance among the uropathogenic strains of *E. coli* have increased worldwide. Recent large international studies of the in vitro susceptibility of *E. coli* strains that cause uncomplicated urinary tract infection [4, 5] have revealed rates of resistance to amoxicillin and trimethoprim–sulfamethoxazole of 20% or higher. These rates of resistance are common worldwide. Rates of resistance to other

agents used for UC such as fluoroquinolones, oral cephalosporins, and amoxicillin–clavulanate are generally lower than 10%, but resistance to the fluoroquinolones is increasing worldwide [6, 7].
Beside the increase of antimicrobial resistance, the "ecological adverse effects" of the antibiotics used in UC have been claimed, especially for a prolonged course of fluoroquinolones. In fact these drugs used for a long period may cause changes in microbioma and may select resistant strains as well. Therefore shortened duration of antibiotic therapy for UC has been proposed in order to reduce the "ecological adverse effect" [8].

DIAGNOSIS

Clinical diagnosis
Because the diagnosis of UC is almost always done based on a clinical point of view which could be done also by phone, there are several key questions that may help to carry out this diagnosis:

Key question for clinical diagnosis of UC.
Patients with UC should have the following characteristics.
Adult women with acute onset and at least 1 of the following symptoms:
dysuria,
frequency,
urgency,
gross hematuria.

Questions useful for the clinical diagnosis:
Are you in menopause?
Have you uncontrolled diabetes?
Have you fever?
Have you flank pain?
Are you pregnant?
Are you immune depressed?
Have you voiding abnormalities?
Have you a new sex partner?
Have you a sexually transmitted disease?
Have you vaginal symptoms?
Did you have recent urinary tract infections?
Did you have recent urological procedure?
If the answers to the questions are all no; UC diagnosis is highly probable.

Epidemiology of UC
E. coli is the predominant pathogen, while in sexually active women *S. saprophyticus* may cause as many as 25% of episodes of bacterial cystitis in the spring and summer months. *Proteus mirabilis* is also encountered in general practice and should always raise the question of underlying urinary tract calculi. A single bacterial species is responsible for 95% of all episodes of UC [1].
Local antimicrobial susceptibility patterns of *E. coli* in particular should be considered in empirical antimicrobial selection for UC. Since the resistance patterns of *E. coli* strains causing UC varies considerably between regions and countries, a specific treatment recommendation may not be universally suitable for all regions or countries. Resistance rates for all antimicrobials were higher in US medical centers than in Canadian medical centers and were usually higher in Portugal and Spain than other European countries [4]. In general, resistance rates >20% were reported in all regions for ampicillin, and in many countries and regions for trimethoprim/sulfamethoxazole. Fluoroquinolone resistance rates were still <10% in most parts of North America and Europe, but there was a clear trend for increasing resistance compared with previous years [5, 9].
In the ECO-Sens study performed in 5 countries in Europe in the year 2007-2008, studying UC, the authors have found different levels of resistance according to the country of isolation. MDR were more frequent in Greece and Portugal, however MDR were extremely low in UK, Sweden and Austria. The resistance rate, in the previous mentioned countries, in *E. coli* was 2-8,9% for amoxicillin-clavulanate, 0,5-7,6% for ciprofloxacin, 21-34% for ampicillin, 21,2-31,3%

for sulfamethoxazole. So this study confirms that, also in countries with a high incidence of MDR, fluoroquinolone resistance in UC is still under 10%, It is true that from the first ECO-SENS of 1999-2000 the mean rate of fluoroquinolone resistance is increased from 1,1% to 3,9% by the second. Instead resistance to sulfamethoxazole is higher than 20%, the threshold of dangerous resistance [4, 10]. Resistance rate of urinary pathogens to fosfomycin is still low in the community but is increasing among nosocomial pathogens [11].

DIFFERENTIAL DIAGNOSIS

Asymptomatic bacteriuria

Asymptomatic bacteriuria, defined as the presence of bacteria in the urine of an individual without signs or symptoms of a urinary tract infection [12], is thought to be present in 3%-5% of young healthy women and is more common in patients with diabetes and elderly persons [13]. In the majority of cases, even if it is not recommended, asymptomatic bacteriuria is treated with poor results and occasionally can allow the development of a selection of multidrug-resistant bacteria [14]. Recently Cai et al. have demonstrated that asymptomatic bacteriuria treatment is associated with a higher occurrence of antibiotic-resistant bacteria, indicating that asymptomatic bacteriuria treatment is potentially dangerous [15-17]. Asymptomatic bacteriuria shows indications to be treated only during pregnancy.

UC Antibiotic Therapy

For many investigators, traditional dosage regimens for UC are eccessive. Ideally a patient should be treated with the shortest course of the safest and less expensive drug that will eradicate the causative organism. The adverse effect of the drug chosen should be weighed against the severity of the illness.

Many women with cystitis will stop their prescribed treatment when their symptoms are resolved. This is often after the first few doses and it explains why these women often have a supply of antimicrobial agents available at home.

Furthermore, the compliance of patients with drugs administered many times during the day might be low. The regimens for UC should be as simple as possible. There is a strong ecological argument that a patient should be treated with the possible shortest regimen in order to discourage the development of bacterial resistance. Therefore it is suggested that there is no benefit in extending treatment of bacterial cystitis beyond 3 days [18].

Amoxicillin remains the drug of choice for treating *Enterococcus faecalis*. There is some concern about the role of beta-lactams as a group for UC. The results are inferior, clinical response slower, relapse rate higher, and the side effects more troublesome [1].

Trimethoprim-sulfamethoxazole (160/800 mg [1 double- strength tablet] twice-daily for 3 days) is an appropriate choice for therapy, given its efficacy if local resistance rates do not exceed 20%. The threshold of 20% as the resistance prevalence at which the agent is no longer recommended for empirical treatment of acute UC [19].

Fosfomycin trometamol (3 g in a single dose or two-days regimen), where it is available is an appropriate choice for therapy due to minimal resistance and propensity for collateral damage, but it appears to have inferior efficacy compared with fluoroquinolones [20]. Furthermore fosfomycin should be reserved for important uses in countries where nosocomial outbreaks of carbapenem-resistant *Klebsiella pneumoniae* (KPC) are ongoing, because many KPC isolated from UTI are still susceptible to fosfomycin. Therefore the use of fosfomycin for UC should be considered also for "collateral damage" as selection of resistance in most important nosocomial patho-

gens. This concept should be applied to fosfomycin more than to fluoroquinolones [21, 22]. Fosfomycin has also a high rate of emergence of resistance when used alone against *Enterobacteria* [23]. Fosfomycin is active against bacteria in the planktonic phase in urine but not against bacteria that adhere to the epithelial cells or are included inside these cells and therefore relapses might be more frequent [23].

Nitrofurantoin remains a valuable drug, although it is ineffective against *Proteus mirabilis.* Unfortunately the manufacturers in the past have promoted this drug for use in a dose of 100 mg every 6 h for five days, which frequently causes nausea or vomiting. Repeated studies over the past decades have shown the same efficacy and minimal side effects with 50 mg 8-hourly for five days. A macrocrystalline formulation of nitrofurantoin is associated with fewer gastrointestinal side effects, and a dose of 100 mg every 12 hours is currently recommended [1].

Fluoroquinolones are the most studied antibiotic for UC. Ciprofloxacin 250 mg b.i.d for 3 days was as effective as ciprofloxacin given for 7 days, using the same regimen [1]. In order to understand differences among fluoroquinolones used in UTI, not only UC, prulifloxacin was tested in comparison with ciprofloxacin 500 mg every 12 h. Microbiological eradication was achieved in 97% of patients treated with prulifloxacin and ciprofloxacin, but at the early follow-up, the rate of patients showing successful treatment was 90.8% in the prulifloxacin group, and 77.8% in the ciprofloxacin group (p=0.008). Clinical success rates at 5-7 days (98,1% vs 98,2%) and at 30 days (97,1% vs 96,3%) after prulifloxacin or ciprofloxacin therapy were similar [24].

Among the fluoroquinolones, prulifloxacin and levofloxacin have a very broad spectrum of antimicrobial activity, which covers both Gram-positive and Gram-negative, including *P. aeruginosa*. Prior studies have shown that prulifloxacin has very potent in vitro antimicrobial activity against Gram-negative pathogens and more potent than levofloxacin [25]. The prulifloxacin MICs and minimum bactericidal concentrations tend to be equal or even lower compared with ciprofloxacin, while they are generally lower compared with levofloxacin, for most Gram-negative pathogens, including *P. aeruginosa*. The mutant prevention concentration of prulifloxacin has also been shown to be lower in comparison with other relevant fluoroquinolones for both *E. coli* and *P. aeruginosa* [26, 27]. This ability to prevent the generation of resistant strains might be very useful in case of single dose treatment of UC. Regarding specifically the urinary tract pathogens studied, prulifloxacin had more potent activity than levofloxacin against the uro-pathogens and more potent activity than ciprofloxacin against *P. mirabilis* and *S. saprophyticus*. Fluoroquinolones are more effective than amoxicillin/clavulanate and cotrimoxazole [1].

Single dose therapy

The single dose strategy might be accepted more favorably by patients, might have less adverse events (e.g. rashes, gastrointestinal symptoms, vaginal candidiasis), it may reduce the cost of treatment and might reduce antibiotic pressure and therefore the collateral damage on isolation of MDR microorganisms.

A woman that is treated successfully with single dose therapy is unlikely to have a urinary tract abnormality [28]. The practical consequence of this is that only those women who are single-dose failures warrant a prolonged antibiotic therapy and/or urinary tract investigation [29].

The patients should be instructed to return only if the symptoms failed to be resolved or they recurred shortly after finishing treatment and in this case urine culture could be useful [30].

Table 1 - Pharmacokynetic parameters of ulifloxacin after administration of a sigle dose of 600 mg of prulifloxacin.

C_{max}	t_{max}	$t_{1/2}$
1,6 µg/ml	1 h	10,7 h

Prulifloxacin 600 mg/day single dose was compared with pefloxacin 800 mg/day single dose in 239 women with UC [31]. The microbiological eradication was similar in both treatment arms (97% vs 96%). The clinical efficacy rate was also similar with only 7,8% and 15,7% failure in the prulifloxacin and pefloxacin-treated patients respectively, these results were confirmed after 30 days [31].
Prulifloxacin with its long half-life (10,7 hours), favorable C max 1,6 mg/L (*Tab. 1*) and long post-antibiotic effect, including a potent anti-gram negative activity might be the right solution for a single tablet therapy for UC. Furthermore prulifloxacin is not active against anaerobes and it might have less impact on fecal microbioma thus being useful in reducing the incidence of *C. difficile* colitis and selection of MDR gram-negative. In English literature, so far, there are no cases of *C. difficile* associated to prulifloxacin use [32].
Fluoroquinolones are the most frequently used drugs to treat UC [33]. Therefore in this class of antibiotic; a drug with the above mentioned characteristics such as prulifloxacin may be very useful. UC is a bladder infection that involves all mucosa layers, therefore the drugs of choice have to penetrate the deeper layers of bladder. This may be the reason why fosfomycin may be less effective than quinolones in the treatment of UC. In case of failure of eradication of the microorganism from the bladder, the epithelial layer may be further damaged and subsequent relapse or recurrence might occur [34].
Early clinical and microbiological efficacy of different classes of antimicrobial in UC, in single dose or in multiple dose regimens are listed in *table 2*. In table 2 are listed the drugs used for single dose therapy.

Antimicrobial stewardship
Although principles of appropriate use of antibiotics have been encouraged since the introduction of antimicrobials, now they are more urgent than ever. The antimicrobial stewardship programs (ASP) have been designed to improve antibiotic prescription and they have proven highly successful in improving antibiotic use, although their impact has been difficult to measure [35]. Effective ASP might have an impact on antibiotic selection and duration in UTI [36].
ASPs are necessary, not only in the hospital, but also in the community, in fact MDR microorganism are no longer limited to health care settings [37].

Table 2 - Early efficacy of different treatment for UC.

Drug	Dose	Mean age of women included in the studies	Early clinical efficacy %	Early microbiological efficacy
Cotrimoxazole	160/800 mg b.i.d for 3-7days	32 (18-58)	91 (86-100)	91 (85-100)
Nitrofurantoin	100 mg b.i.d.for 5-7days	35 (16-89)	92 (87-95)	87 (82-92)
Fosfomycin	3 g sigle dose	38 (15-92)	91 (83-95)	83 (78-98)
Fluoroquinolone	Variable (3-7 days)	35 (18-89)	90 (81-98)	91 (78-96)
Fluoroquinolone single dose	Ciprofloxacin 500 mg Prulifloxacina 600 mg Pefloxacina 800 mg	18-65 25-47 25-47	91 92 84	91 97 92
Beta-lactams	Variable (3 days)	30 (18-59)	86 (79-98)	81 (74-98)

One of the most common infections encountered in emergency departments (ED) and in the community is urinary tract infections (UTIs).
These common infections are managed in both in- and outpatient settings, and ED practitioners and general practitioner (GP) are involved with establishing empiric and definitive treatment.
Antimicrobial over-prescribing in the ED and community determines "collateral damage" also in the community. Therefore, ED and general practitioners are important targets for ASP initiatives in order to produce beneficial effects in the community.
Asymptomatic bacteriuria (ASB) does not require antibiotic treatment [38]. UTI diagnosis based on a urinalysis (UA) or dipstick alone in the absence of symptoms leads to overuse of antibiotics [39]. UC might be another field of application of ASP in ED and community.
In fact UC does not need microbiology and the diagnosis is only based on clinical judgment. In the past pharmaceutical companies have pushed for longer therapy in order to avoid failure but with more incidence of adverse effects and selection of resistance. Prulifloxacin might be an important agent to use for ASP in the community. From our perspective, it is useful that a pharmaceutical company support a shorter treatment for UTI.

Panel conclusion
Episodes of acute cystitis occurring occasionally in healthy pre-menopausal, non-pregnant women, with no history suggestive of an abnormal urinary tract, are generally classified as UC. The diagnosis of UC is clinical. Laboratory examination is not necessary. If the patient's problems are not resolved by a single tablet therapy, further investigation will be necessary, including urinalysis, urine culture and study of the urinary tract.
Among the fluoroquinolones, prulifloxacin has a very broad spectrum of antimicrobial activity, which covers both Gram-positive and Gram-negative aerobes, including *E. coli*. Prulifloxacin was approved for single dose therapy for UC in Italy, due to its long half-life and long post-antibiotic effect. Because it has no activity against anaerobes, its effect on fecal microbioma might be less important with respect to other fluoroquinolone. In conclusion UC might be treated with a single dose of an effective fluoroquinolone such as prulifloxacin.
Patients may better accept the use of a single dose therapy that may have less adverse effects, less impact on gut microbioma and also it might be less expensive. In an antimicrobial stewardship program of the community, a single dose therapy for UC may have a positive ecological impact.

Acknowledgments
There is no conflict of interest for each of the authors.
In the past 2 years, C.T. has been paid for lectures on behalf of Astellas, Angelini, Gilead, Pfizer, Novartis and Merck.

REFERENCES

[1] Gupta K., Hooton T.M., Naber K.G., et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the infectious diseases society of America and the european society for microbiology and infectious diseases. *Clin. Infect. Dis.* 52, e103-e120, 2011.
[2] Grigoryan L., Trautner B.W., Gupta K. Diagnosis and management of urinary tract infections in the outpatient setting: a review. *JAMA* 312, 1677-1684, 2014.
[3] Warren J.W., Abrutyn E., Hebel J.R., Johnson J.R., Schaeffer A.J., Stamm W.E. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). *Clin. Infect. Dis.* 29, 745-758, 1999.
[4] Kahlmeter G. An international survey of the antimicrobial susceptibility of pathogen from

uncomplicated urinary tract infections: the ECO. SENS Project. *J. Antimicrob. Chemother.* 51, 69-76, 2003.
[5] Naber K.G., Schito G., Botta H., 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.* 54, 1164-1175, 2008.
[6] Brown P.D., Freeman A., Foxman B. Prevalence and predictors of trimethoprim-sulfamethoxazole resistance among uropathogenic *Escherichia coli* isolates in Michigan. *Clin. Infect. Dis.* 34, 1061-6, 2002.
[7] Metlay JP, Strom BL, Asch DA. Prior antimicrobial drug exposure: a risk factor for trimethoprim-sulfamethoxazole-resistant urinary tract infections. *J. Antimicrob. Chemother*. 51, 963-70, 2003.
[8] Paterson D.L. "Collateral damage" from cephalosporin or quinolone antibiotic therapy. *Clin. Infect. Dis.* 38 (Suppl. 4), S341-S345, 2004.
[10] Zhanel G.G., Hisanaga T.L., Laing N.M., et al. Antibiotic resistance in *Escherichia coli* outpatient urinary isolates: final results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA). *Int. J. Antimicrob. Agents.* 27, 468-475, 2006
[11] Khalmeter G., Poulsen H.O. Antimicrobial susceptibility of *E. coli* from community-acquired urinary tract infections in Europe: the ECO-SENS study revisited. *Int. J. Antimicrob. Agents.* 39, 45-51, 2012.
[12] Demir T., Buyukguclu T. Evaluation of the in vitro activity of fosfomycin tromethamine against gram-negative bacterial strains recovered from community- and hospital-acquired urinary tract infections in Turkey. *Int J Infect Dis.* 17, e966-e970, 2013.
[13] Hooton T.M., Scholes D., Stapleton A.E., et al. A prospective study of asymptomatic bacteriuria in sexually active young women. *N. Engl. J. Med.* 343, 992-997, 2000.
[14] Raz R. Asymptomatic bacteriuria: clinical significance and management. *Int. J. Antimicrob. Agents.* 22 (Suppl. 2), S45-S47, 2003.
[15] French GL. The continuing crisis in antibiotic resistance. *Int. J. Antimicrob. Agents.* 36 (Suppl. 3), S3-S7, 2010.
[16] Cai T., Nesi G., Mazzoli S., et al. Asymptomatic bacteriuria treatment is associated with a higher prevalence of antibiotic resistant strains in women with urinary tract infections. *Clin. Infect. Dis.* 61, 1655-1661, 2015.
[17] Beerepoot M.A., Geerlings S.E., van Haarst E.P., van Charante N.M., ter Riet G. Nonantibiotic prophylaxis for recurrent urinary tract infections: a systematic review and meta-analysis of randomized controlled trials. *J. Urol.* 190, 1981-1989, 2013.
[18] Sundqvist M., Geli P., Andersson D.I., et al. Little evidence for reversibility of trimethoprim resistance after a drastic reduction in trimethoprim use. *J. Antimicrob. Chemother.* 65, 350-360, 2010.
[19] Elder M.C. Acute urinary tract infection in women: what kind of antibiotic therapy is optimal? *Postgrad. Med.* 92, 159-172, 1992.
[20] Gordon K.A, Jones R.N., Sentry partecipants group (Euope, Latin America, North America. Susceptibility patterns of orally administered antimicrobials among urinary tract infection pathogens from hospitalized patients in North America: comparison report to Europe and Latin America. Results from the Sentry Antimicrobial Surveillance Program (2000). *Diagn Microbiol Infect Dis.* 45, 295-301, 2003.
[21] Fosfomycin for urinary tract infections. *Med. Lett. Drugs. Ther.* 39, 66-68, 1997.
[22] Alexander B.T., Marschall J., Tibbetts R.J., Neuner E.A., Dunne W.M. Jr, Ritchie D.J. Treatment and clinical outcomes of urinary tract infections caused by KPC-producing *Enterobacteriaceae* in a retrospective cohort. *Clin. Ther.* 34, 1314-1323, 2012.
[23] Da Silva J.O., Yu M.C., Doi A., de Araujo M.R., Neto P. A., Furtado G.H. Successful treatment of lower urinary tract infections with oral fosfomycin: a report of three cases. *Rev. Soc. Bras. Med. Trop.* 48, 358-60, 2015.
[24] Docobo-Perez F., Drusano G.L., Johnson A., et al. Pharmacodynamics of fosfomycin: insights into clinical use for antimicrobial resistance. *Antimicrob. Agents. Chemother.* 59, 5602-5610, 2015.
[25] Carmignani G., De Rose A.F., Olivieri L., Salvatori E., Rosignoli M.T., Dionisio P. Prulifloxacin versus ciprofloxacin in the treatment of adults with complicated urinary tract infections. *Urol. Int.* 74, 326-331, 2005.
[26] Fritsche T.R., Biedenbach D.J., Jones R.N. (2009). Antimicrobial activity of prulifloxacin test-

ed against a worldwide collection of gastroenteritis-producing pathogens, including those causing traveler's diarrhea. *Antimicrob. Agents. Chemother.* 53, 1221-1224, 2009.
[27] Giannarini G., Tascini C., Selli C. Prulifloxacin: clinical studies of a broad-spectrum quinolone agent. *Future. Microbiol.* 4, 13-24, 2009.
[28] Prats G., Roig C., Miró E., Navarro F., Mirelis B. (2002) In vitro activity of the active metabolite of prulifloxacin (AF 3013) compared with six other fluoroquinolones. *Eur. J. Clin. Microbiol. Infect. Dis.* 21, 328-334, 2002.
[29] Bailey R.R. Single oral dose treatment of uncomplicated urinary tract infection in women. *Chemotherapy.* 42, (Suppl. 1) S10-S16, 1996.
[30] Bailey R.R. Management of uncomplicated urinary tract infections. *Int. J. Antimicrob. Agents.* 4, 95-100, 1994.
[31] Bailey R.R., Gorrie S., Peddie B.A., Davies P.R. Double blind randomized trial comparing single dose enoxacin and trimethoprim for treatment for treatment of bacterial cysititis. *N. Zel. Med. J.* 100, 618-619, 1987.
[32] Cervigni M., Orticelli G, Bolognas M., et al. Single dose prulifloxacin versus single dose pefloxacin in the treatment of acute uncomplicated urinary tract infection in women. *Urogynaecol. Internat. J.* 17, 69-77, 2003.
[33] http://www.ncbi.nlm.nih.gov/pubmed. Last access february 1th 2016.
[34] Kallen A.J., Welch H.G., Sirovich B.E. Current antibiotic therapy for isolated urinary tract infections in women. *Arch. Intern. Med.* 166, 635-639, 2006.
[35] Bassetti M., Costantini E. Le infezioni delle basse vie urinarie. Percorsi diagnostico-terapeutici. 2012, 20-22. Percorsi Editoriali di Carocci editore, Roma
[36] File T.M. Jr, Srinivasan A., Bartlett J.G. Antimicrobial Stewardship: Importance for Patient and Public Health. *Clin. Infect. Dis.* 59 (Suppl. 3), S93-96, 2014.
[37] Thompson C.A. CMS reveals Medicare's value-based purchasing program for hospitals. *Am. J. Health. Syst. Pharm.* 68, 1062-1071, 2011.
[38] Moran G.J., Krishnadasan A., Gorwitz R.J., et al. Methicillin-resistant *S. aureus* infections among patients in the emergency department. *N. Engl. J. Med.* 355, 666-674, 2006.
[39] Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States. 2013. http://www.cdc.gov/drugresistance/pdf/ar- threats-2013-508.pdf. Accessed 28 March 2015.
[40] Pallin D.J., Ronan C., Montazeri K., et al. Urinalysis in acute care of adults: pitfalls in testing and interpreting results. *Open. Forum. Infect. Dis.* 1, ofu019, 2014.