Evaluation of the Hungarian ambulatory antibacterial use in urinary tract infections with different methods

Ph.D. Thesis

Zoltán Juhász M.D.

Supervisor:

Edit Hajdú M.D., Ph.D.

Doctoral School of Interdisciplinary Medicine

Divison of Infectious Diseases, 1st Department of Internal Medicine
Albert Szent-Györgyi Health Centre
University of Szeged

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II. **Juhász Z**, Benkő R, Matuz M, Viola R, Soós G, Hajdú E.: Az akut cystitis kezelésének hazai gyakorlata országos vényforgalmi adatok alapján. *Orv Hetil.* 2014; 15:590-596.

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IV. **Juhász Zoltán**, Benkő Ria, Matuz Mária, Hajdú Edit: Cystitis kezelése Magyarországon: a hazai ajánlások és az ESAC minőségi indikátorok összevetése. A Magyar Infektológiai és Klinikai Mikrobiológiai Társaság Tudományos Ülése. Budapest, 2012. június 7.

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LIST OF ABBREVIATIONS

ACC	Acute complicated cystitis
ATC	Anatomical Therapeutic Chemical
AUC	Acute uncomplicated cystitis
AUP	Acute uncomplicated pyelonephritis
DDD	Defined daily dose
ECDC	European Centre for Disease Control and Prevention
ESAC	European Surveillance of Antimicrobial Consumption
ESBL	Extended spectrum beta-lactamase
EuroDURG	European Drug Utilization Research Group
FMT	Fosfomycin-trometamol
GP	General practitioner
ICD	International Classification of Diseases
ICPC-2R	International Classification of Primary Care, second revision
IDSA	Infectious Diseases Society of America
nrAUC	Non-recurrent acute uncomplicated urinary tract infection
OGYI	Országos Gyógyszerészeti Intézet
OGYÉI	Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet
OÉTI	Országos Élelmezés- és Táplálkozás-egészségügyi Intézet
rAUC	Recurrent acute uncomplicated urinary tract infection
TESSy	The European Surveillance System
TMP-SMX	Trimethoprim-sulfamethoxazol
UTI	Urinary tract infection
uUTI	Uncomplicated urinary tract infection
WHO	World Health Organization

1. INTRODUCTION

One of the most important public health achievements of the XX. century was the discovery of antimicrobial agents. Since then mortality rates of infectious diseases decreased considerably in high-income countries [1]. After the discovery of penicillin in 1929, until 1950 more than 100 antibiotics were known [2,3,4].

In the 1950s-60s following the „golden era" of antimicrobials emerged many problems including biological, medical, economical and scientific challenges in relation to the widespread of the agents [4]. The resistance of bacteria to antibiotic was first recognized since the early 1940s and in spite of several reports and internationally published data continued to spread [5,6]. Drug resistant strains appeared first in hospitals where most antibiotic were administered initially [6,7]. Multidrug resistant bacteria were first detected among enteric pathogens (eg. *E.coli*) in late 1950s [8,9]. Nowadays increased resistance and virulence of pathogens became an international challenge for countries in the world. The inappropriate and excessive use of antibiotics for the treatment and prophylaxis of infectious diseases are the main drivers of the selection pressure by killing the susceptible strains and selecting the resistant ones [6,10-12]. Most antibiotics are used unnecessarily and by physicians uncertain of diagnosis or treating self-limiting bacterial or viral infections [13].

Antibiotic resistance limits the available treatment options and causes increased morbidity and mortality as well as increased costs because of the failure of the empirical therapy [14,15]. Approximately 25 000 people die every year in Europe from antibiotic resistant bacteria and 23 000 deaths are caused by resistant bacteria in the USA every year [13,16,17].

High income countries like Sweden, France and the UK succeeded in reducing their antibiotic consumption through better prescription practices without recorded measurable harm [14,18,19]. Globally, the largest absolute increases in consumption between 2000 and 2010 were observed for cephalosporins, broad-spectrum penicillins and fluoroquinolones. The most important relative increase since 2010 were described for fluoroquinolones (64%), cephalosporins (93%) [20]. The increase of antibiotic consumption may be due to demographic as well as economic growth, increased health expenditure and increased availability of antibiotics in the market [10,21,22].

Most important motivation for selecting an antibiotic besides resistance are pharmacodynamic, pharmacokinetic and tolerability aspects [15,23,24].

The antibiotic consumption varies greatly among the European countries. The mean antibacterial consumption rate in the community was 21.5 defined daily dose (DDD) per 1000 inhabitants per day in the EU/EEA countries (17.5% increase since 2010), ranging from 11.3 DDD per 1000 inhabitants per day in the Netherland to 31.9 DDD per 1000 inhabitants per day in Greece [25].

As Figure 1 shows the outpatient antibiotic consumption rate in Hungary is placed in the lower third of the EU/EEA countries with 13.8 DDD per 1000 inhabitants per day [25].

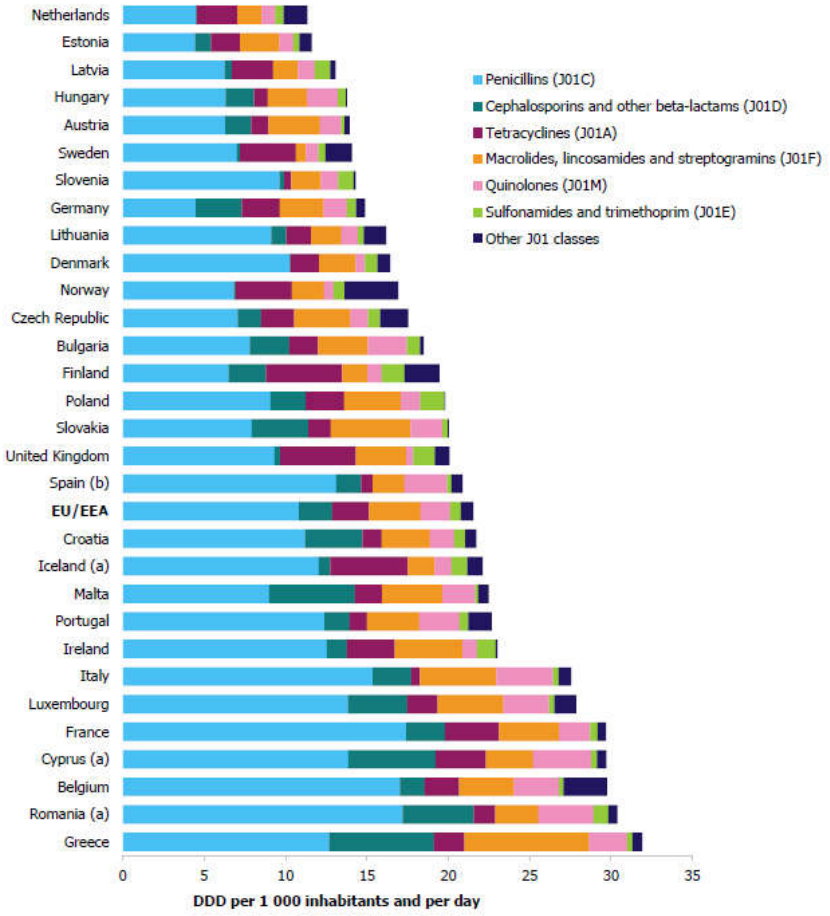


Figure 1. Consumption of antibacterials for systemic use in EU/EEA countries, 2012 (expressed as DDD per 1 000 inhabitants and per day) [25]

The use of quinolones is relatively high in Europe, it was in the third quartile among the EU countries in 2009, the ambulatory antibiotic consumption fourth quartile similarly to the South-European countries. The consumption of quinolones tripled between 1996 and 2012 in Hungary in ambulatory care (0.64 vs. 1.91 DDD per 1000 inhabitants per day) and shared

more than 10% from the ambulatory antibiotic consumption [26]. Figure 2 demonstrates the consumption of quinolones for systemic use in the ambulatory care in 2012.

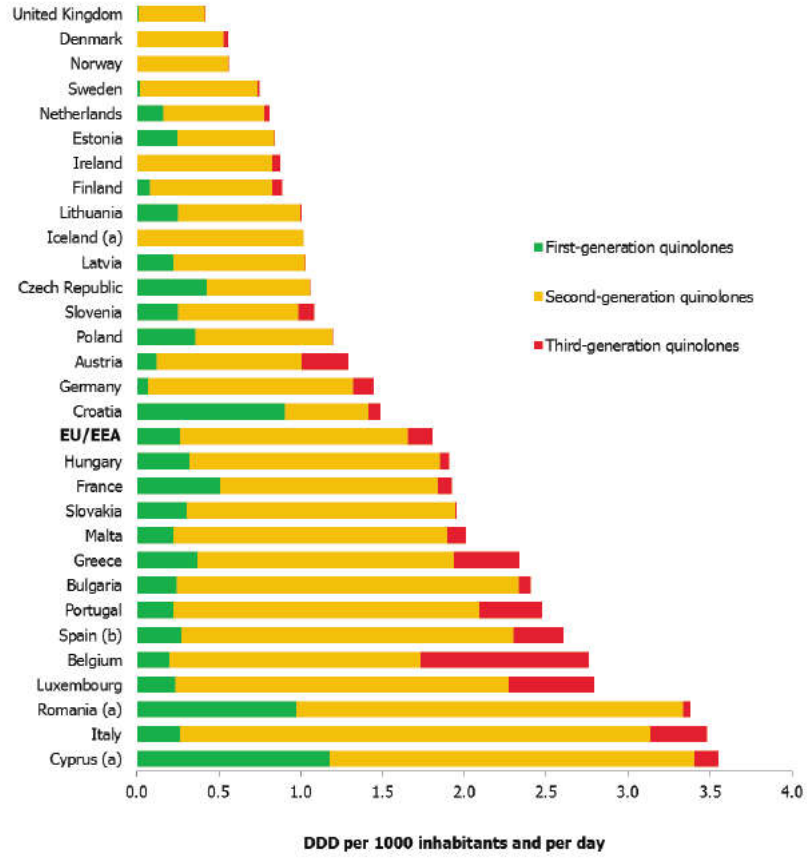


Figure 2. Consumption of first-, second- and third-generation quinolones for systemic use in the community, EU/EEA countries in 2012 (expressed as DDD per 1 000 inhabitants and per day) [25]

The largest volume of antibiotics for systemic use are prescribed in the primary care. The second most common indication for antibiotic use – following the respiratory tract infections – are the urinary tract infections, where antibiotics are usually prescribed in more than 85% of cases [29-33].

During the last decade the isolation of extended-spectrum-beta-lactamase-(ESBL)-producing *E.coli* and *K. pneumoniae* from urinary tract infection has been increasingly reported in the hospital care from all over the world [15,23]. It is a worrisome fact that these strains have also appeared in the community that outlines the importance of rational antibiotic prescription practice [32-34].

The antibiotic consumption can be evaluated through prescription databases and patient-level data at different levels (national, regional) with the means of pharmacoepidemiology.

The aim of my Ph.D. work was to assess ambulatory antibiotic use in urinary tract infections in Hungary by applying these approaches.

2. BACKGROUND

2.1. Pharmacoepidemiology and drug utilization studies

Pharmacoepidemiology is defined as an epidemiological approach to drug issues to assess how these drug function in the population. It is the study of therapeutic effects, use of drugs, risk of utilization examined usually in large populations with the methods of epidemiology and /or reasoning [35,36].

Pharmacoepidemiology research may be divided into two main fields:

1. investigations of variation in drug use in the population, drug prescription pattern, identifying of predictors for use and providing explanatory hypotheses.

2. describing adverse drug effects, post marketing studies evaluating long-term effects of specific drugs in the population by case-control and cohort studies [35].

The basic aim of the pharmacoepidemiological study is to describe a situation in real life applying descriptive as well as etiologic approaches, but avoiding any modification [36].

The supporting of the rational and cost-effective drug use in the population leads to the improvement in health outcomes [37]. There are increasing international concerns that many prescribing may be unnecessary or irrational (overuse of certain type of drugs) and not without dangers [38-42]. Common problems identified in hospital and ambulatory care could contribute to antibiotic resistance and poor outcomes of patients, decreasing the quality of healthcare [43].

The drug utilization as a research field enables investigating drug prescribing and usage from a scientific point of view. Drug utilization has been defined by WHO as the „marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social, economic consequences” [38,44]. Studies on drug utilization are qualitative or quantitative.

Quantitative data are collected about the variablity and extent of drug usage and the cost of therapy. Drug utilization studies provide data also for further qualitative research, and adherence to therapeutic guidelines can also be determined [44-48].

The main goals of drug utilization studies are:

- investigation of cost-effectiveness and benefit-risk
- indicating overuse, underuse of a single drug, or classes of drugs
- identifying problems or fields on the efficacy or safety of drug therapy that needs to be evaluated by further studies [44].

Information from drug utlization statistics could be used by national health systems, universities, drug information centres [49]. Drug utilization studies have great value of assessment of prevalnce and importance of inappropriate prescribing pattern and indicate the need for interventions among physicians [38]. These purposes all serve the improvement of the quality of health care.

The common classification system for drugs was developed after a WHO symposium on Consumption of drugs in Oslo in 1969. A small group of experts mainly from Northern Europe worked out the anatomical therapeutic chemical (ATC) classification system for drugs and the defined daily dose (DDD) as a comparative unit of drug use. Since then the cross-national drug utilization studies were based on the ATC/DDD methodology [50].

The purpose of the ATC/DDD system is to serve as a tool for drug utilization research to improve the quality of drug use. The ATC/DDD system itself is not suitable for guiding decisions about reimbursement, pricing, therapeutic substitution. It is not a recommendation for use or efficacy of drugs [49].

The first study applying ATC/DDD methodology appeared in 1975 and described differences between the investigated areas in the use of insulin and antidiabetic drugs [51].

Interestingly, the formal European Drug Utilization Research Group (EuroDURG) held its initial meeting in Hungary in 1996. Applying the ATC/DDD methodology cross-national EuroDURG studies contributed to the improvement of drug-utilization. The international

comparisons helped to identify markers and indicators of differences regarding the quality of drug prescription at each level [52-55].

In the ATC classification system the drugs are divided into different according to the target organs, therapeutical, pharmaceutical and chemical attributions.

Five different levels exists when the drugs are classified,

1st level: anatomical main group

2 st level: therapeutic subgroup

3rd level: pharmacological subgroup

4th level: chemical subgroup

5th level: chemical substance

For example, ***antibacterials for systemic use*** belong to J01 group. J01M indicates ***quinolone*** antibacterials, J01MA signs ***fluoroquinolones***, J01 MA02 ***ciprofloxacin*** [37,49].

Defined daily dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults, part of the ATC/DDD scheme for international comparison of drug utilization. It is a unit of measurement that does not reflect the recommended or prescribed daily dose. Drug consumption data in DDDs only give rough estimate of consumption and not an exact picture of actual use.

Since the number of units sold is expressed is expressed in the form of a common reference, it DDD is enabling the researcher to assess trends in drug consumption and to perform comparisons between population groups. DDD is assigned for only those drugs that already have an ATC code [36,49].

Drug consumption figures should preferably be presented as numbers of DDDs/1000 inhabitants/day or in hospital drug consumption DDDs per 100 bed days.

DDD/1000 inhabitants/day may provide a rough estimate of the proportion of the population within a defined area treated with certain drugs [40].

ATC/DDD system can be used for drug utilization statistics in a variety of settings (primary care, hospital care) from a variety of sources:

- ***official sources*** (eg. health insurance companies)

- ***pharmaceutical companies***

- ***records from pharmacies***

- ***health facility data from hospital or primary care physicians***: provide valuable patient-level data on the prescribing of drugs related to the patient's age, sex, employment, social status, underlying diseases. However, the age and training of medical practitioners, traits of the practices, influence of pharmaceutical salesman could also be investigated [38,49].

The clinical guidelines are developed to close gaps between resarch and practice, the evidence and applicability must always be considered when formulating these recommendations [56]. Appropriate implementation strategies are needed when the recommendation are not compatible with the existing clinical practice [56].

Practice guidelines are important means of healthcare quality improvement in many European countries [57]. Incorrect use of antibiotics and non-adherence to national antibiotic guidelines are major public health concerns globally because of the development of antibiotic resistance. The investigation of the adherence rate to these guidelines could provide further information on the quality of antibiotic consumption. Measurability provides great opportunity for national and international comparisons.

It is usually not enough to measure the consumption of the medications, we also have to measure its quality. Introducing and applying quality indicators may help researchers to describe and compare the use of drugs in certain types of diseases.

2.2. Quality indicators

Quality indicators are focusing on different aspects of quality: effectiveness, safety, appropriateness, costs, compliance and persistance and should be relevant for clinical practice [58-60].

Quality indicators can be categorized on ***two axes***:

1. structures (eg. staff, equipment); processes (eg. prescribing); outcomes (eg. morbidity, mortality)
2. patient-, drug-, disease-specific indicators [58,61].

Drug-specific indicators refer only about drugs, whereas disease-specific indicators provide information on drugs linked to a diagnosis, quality of prescribing is considered part of the whole treatment process quality [62]. ***Patient-oriented indicators*** provide clinical information about the patient, eg. course of the disease [62]. Most quality indicators have been developed for hospital settings [63-65], but they are increasingly used in the outpatient care [66-69].

Prescribing quality indicators are measurable elements of prescribing performance for which there is evidence or consensus that they can be used to assess and change the quality of health care [60,62]. Prescribing quality indicators are defined as „a percentage of patients who received the recommended drug treatment, with numerator comprising the number actually receiving the treatment and denominator comprising the number of all patients for whom the treatment is appropriate"[70].

Prescribing quality indicators have defined criteria of what constitutes good quality of care and the values of the indicators that should be reached.

Indicators of appropriateness of prescribing should have a central role in evaluating the performance of general practitioners and encouraging/promoting improvements in the quality of care. They should cover major elements of practice and should be workd out with the help of general practitioners [60].

The main reasons for developing prescribing quality indicators include:

- the good prescribing practice is an important issue in the quality of care
- the reduction of healthcare costs associated with the poor prescribing including side effects and interactions
- the necessity of proxies giving an indication of performance [60].

Prescribing quality indicators reflect the efforts of appropriate prescribing practice and used only for guidance: they cannot provide clear evidence of success or failure and they are suitable for raising questions instead of providing answers [60,71].

Indicators demonstrate potential problems and appropriate changes in prescribing should be captured. Quality indicators must be interpreted within the overall improvements in the healthcare system [70,72].

Practical advantage of these indicators was reported from Scotland, where the seasonal variation of quinolone prescription dropped under 5% in most health service boards, thus decreasing the incidence of *Clostridium difficile* infections [73,74]. A study using quality indicators in Hungary were published by *Katona* for respiratory tract infections in primary care [75].

2.3. ESAC

The European Surveillance of Antimicrobial Consumption (ESAC) project started in November 2001. The project was funded by grants of the European Commission and the University of Antwerp, Belgium. From 2007-2011 ESAC project was funded by a grant from the European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden [76].

The main task of ESAC were collecting national antimicrobial consumption data and building a comprehensive and comparable database from the 27 EU member countries, 3 EEA/EFTA countries, the 3 candidate countries (Croatia, former Yugoslav Republic of Macedonia and Turkey) and two non-member countries (Israel, Russian Federation) [76].

In 2004 ESAC introduced subprojects focusing on the following fields:

- in depth study of antimicrobial consumption in the hospital and outpatient care
- analysis of socio-economic determinants of outpatient antibiotic consumption
- web-based point-prevalence surveys of antibiotic prescription in hospitals and long-term care facilities [76].

ESAC project group published data on the trends of outpatient antibiotic use in Europe between 1997-2009 (eg. for penicillin, cephalosporins, quinolone, tetracycline, sulphonamide and trimethoprim, macrolides) [73,77-81].

In 2007 12 valid drug-specific quality indicators were published by ESAC for outpatient antibiotic use in Europe [70]. Based on these drugs-specific quality indicators outpatient antibiotic use was assessed in 2009 in Europe and quality change was also evaluated. It was found that quality of antibiotic use in DID decreased between 2004 and 2009 comparing the Nordic and Southern European countries. Among others the use of quinolones and penicillins (including beta-lactamase inhibitors) in DID increased [73,77,79,82].

However, quality improvement was also observed as the seasonal variation of prescribing total antibiotics and quinolones decreased between 1997 and 2009 [72,73,77].

In 2008 and 2009 ESAC Ambulatory Care Subproject with the participation of 40 experts from 25 countries developed disease-specific quality indicators for the seven most common indications (three for each) for antibiotic prescribing in the primary care [83]. For each of the six main indication for antibiotic prescribing in ambulatory care (acute otitis media, acute upper respiratory infection, acute/chronic sinusitis, acute tonsillitis, acute bronchitis/bronhiolitis, cystitis/other urinary infection) and for pneumonia ***three quality indicators*** were developed:

a. the percentage of patients with age and/or gender limitation prescribed an antibiotic for systemic use

b. the percentage of patients with age and/or gender limitation prescribed an antibiotic for systemic use, and receiving the guideline recommended antibiotic

c. the percentage of patients with age and/or gender limitation prescribed an antibiotic for systemic use, and receiving quinolones

This set was scored by 40 experts from 25 countries. All proposed disease-specific quality indicators for outpatient antibiotic prescribing have face validity and are potentially applicable [70,83]. The disease-specific quality indicators could be used to better describe antibiotic use and assess the quality of national or international antibiotic prescribing pattern in primary care.

Comparison between countries has been considered an important motivation for improvement of quality (eg. antibiotic consumption). This set of disease-specific quality indicators could allow primary care practices, networks, countries to assess their position in relation to others.

Data may reflect valid and important differences in health care quality, eg. inappropriate antibiotic use, that needs further investigation and intervention [83].

Since 2013 the European Surveillance of antimicrobial consumption network (ESAC-Net) covers all EU/EEA countries in agreement with decision 1082/2013/EU of the European Parliament and the Council of 22 October 2013. The organization continues to collect reference data on the consumption of antimicrobials in the hospital sector and in the

community at EU/EEA level through the European Surveillance System (TESSy) maintained at the ECDC [84].

ESAC-Net surveillance of the antimicrobial consumption include the collection of the following data:

- Antibacterials for systemic use (ATC therapeutic subgroup J01)
- Antimycotics for systemic use (ATC therapeutic subgroup J02)
- Antifungals for systemic use (ATC chemical subgroup D01BA)
- Antimycobacterials (ATC pharmacological subgroup J04A)
- Antivirals for systemic use (ATC therapeutic subgroup J05)
- Nitroimidazole derivates used orally and rectally as antiprotozoals (ATC chemical subgroup P01AB)
- Vancomycin used orally as intestinal antiinfective (ATC chemical substance A07AA09).

The data derive from national drug registers, reimbursement and sales data [85].

Antibiotic consumption data are expressed in DDD per 1000 inhabitants per day and the number of packages per 100 inhabitants according to WHO ATC/DDD methodology [84].

ESAC-Net collects and analyses data from national surveillance networks (in Hungary from the National Centre of Epidemiology and University of Szeged) on antimicrobial consumption from the outpatient and hospital care. The published data provide comparisons between countries and regions, analysis of the trends of antibiotic consumption in different ATC groups [85]. The ESAC-Net intractive database spreads information to the public on antimicrobial consumption in Europe and publishing the „Surveillance of antimicrobial consumption in Europe" every year [84,85].

2.4. Hungarian antibiotic studies

In Hungary the ATC/DDD system is adapted by the National Institute of Pharmacy (OGYI) that collects national drug utilization statistics. According to the 28/2015. (II. 25.) ordinate the organization has been recently fused with the National Institute for Food and

Nutrition Science (OÉTI) and the National Institute of Pharmacy and Nutrition (OGYÉI) was established.

Beyond the official drug utilization surveys, only a few researcher carried out and published drug utilization studies [86-89].

Despite the few official national drug utilization surveys, lots of articles appeared in the literature mainly in the 1980s and 1990s focusing on the consumption of antibiotics [90-107].

Some of the publications were reporting from the hospital care [105, 107-112], others from the primary care [87,93,106,113], and some of them from both sectors [88,99-101] some of the works reported about the overall antibiotic consumption [95,98,102,103,114]. Only a few article expressed the antibiotic use in a comparable and standardised unit, DDD per 1000-inhabitant days [95,100,102,103]. National coverage of separate outpatient antibiotic use applying ATC/DDD methodology was first published by *Graber* [95].

The patient-level surveys of *Katona* should be emphasized, as he concentrated on the overuse/misuse and thus the quality of antibiotic use in the primary care, mainly focusing on respiratory care infections [75,93,104,113,115,116].

There are some international [69,117-122] articles and only a few Hungarian [75,123] works dealing with the quality of antibiotic consumption in the ambulatory care, even with prescribing quality indicators [68,75,124-126]. Another important field in connection with the quality of antibiotic use is the adherence of treatment practice to the national clinical guidelines. Publications on first-choice antibiotics complying with national guidelines, demonstrating adherence rates in the outpatient care on the most common infectious diseases (eg. respiratory tract and urinary tract) are scarce in the scientific literature [127-135].

Therefore the drug utilization research in this thesis was motivated by the following considerations:

- Systemic antibiotics play a key role in the outpatients care [27,28]
- The quality of antibiotic use in the Hungarian ambulatory care has been investigated rarely
- Data on the indications of antibiotic consumption in ambulatory care is scarce

- The number of studies using standardised drug consumption units (ATC/DDD methodology) for describing ambulatory antibacterial use linked to an indication is limited

- The possible rate of ambulatory antibiotic misuse in urinary tract infections in Hungary is unknown

- Recent national and regional data on the consumption of antibiotics and treatment practice of urinary tract infections in the primary care are missing

- Insight in national guideline adherence in urinary tract infections is lacking

- Comparing outpatient antibiotic consumption data with ESAC disease-specific quality indicators has never been published in Hungary

- Extensive patient-level data (eg. demographics, data on precribed agents, doses, indication, symptoms, underlying diseases) which enables in-depth analysis of ambulatory antibiotic use in cystitis has never been published in Hungary

2.5. Epidemiology of urinary tract infections

Urinary tract infections (UTI) belong to the most common diseases in the primary care [136]. In the USA UTI accounted for 10.5 million ambulatory visits at the general practitioner in 2007, and 61% of UTI is managed in the primary care settings, representing a significant health care cost of 1.6 billion USD annually [137-141]. More than 80% of the patients were female [140,142]. Economical data relating to the health costs of UTI in Hungary have not yet been published.

Approximately 50% of women report having at least one episode of UTI by the age of 30, the lifetime prevalence is more than 50% [143-145]. The symptoms occur at least once a year in 25% of women aged 20-40 years [146]. Specific populations with increased risk for UTI include infants, elderly, pregnant women, patients with diabetes, underlying urological abnormalities (eg. kidney stones) [140]

There are **non-modifiable** and **modifiable** risk factors that increase the susceptibility to UTI:

- **non-modifiable risk factors**: gender; age; genetic; congential abnormalities

- **modifiable or behavioral risk factors**: use of diaphragms, condom/spermicides for contraception; frequency of sexual intercourse; previous episode of UTI; poor hygenic conditions [140,147-149].

The general risk factors for UTI in males and females are summarized in *Table-1* [150].

Male	Female	Both gender
lack of circumcision	previous urinary tract infection	urologic instrumentation or surgery
prostatic enlargement	pregnancy	urethral catheterization
insertive rectal intercourse	lack of urination after sexual intercourse	urinary tract obstruction, including calculi
vaginal colonization with *E. coli* in partner	diaphragm use	neurogenic bladder
	estrogen deficiency	sexual intercourse
	bladder/vaginal prolapse	functional or mental impairment
		renal transplantation
		diabetes
		immunodeficiency

Table 1. Risk factors for urinary tract infection [150]

In young women the most important risk factors for cystitis include recent or frequent sexual acivity, use of nonoxinol-spermicide and a previous episode of UTI [145,148]. The urinary tract infection may involve the lower urinary tract (cystitis) or both the lower and upper (pyelonephritis) urinary tracts [150].

Urinary tract infections are classified as ***uncomplicated*** or ***complicated*** infections. UTI that occur in a normal genitourinary tract with no prior instrumention is considered uncomplicated, whereas complicated infections are diagnosed in genitourinary tract with functional and/or structural abnormalities (eg. indwelling catheters or other drainage devices, obstruction, immunosuppression, renal failure, renal transplantation and pregnancy) [140,150].

Uncomplicated UTI comprise uncomplicated cystitis and uncomplicated pyelonephritis. A lower UTI is localized to the urinary bladder (cystitis), an upper UTI is localized to the kidneys (pyelonephritis) [151,152]. Acute uncomplicated cystitis, a superficial infection in the bladder mucosa, accounts for the 95% of urinary tract disorders [129,153]. Acute uncomplicated urinary tract infection occur mainly among sexually active, non-pregnant, premenopausal women aged 15-55 years without anatomical and/or functional abnormalities [140,148,154,155]. The recurrence rate is relatively high, at least 25% of women experience a second episode within 6 months of their first UTI [138,140,145,156]. Nonsecretors of the blood group substances have increased frequency of recurrent infection, especially in post-menopausal women. (235) Complicated urinary tract infection occur in both gender and in any age group, any male urinary infection is considered complicated [157,158].

Uropathogen bacteria are assumed to originate primarily from the bowel flora [159]. Among women urinary colonization rates of the urethral opening are higher (1-3% annual incidence in women, whereas only under 0.1% in men), as the rectal opening is closer to the urethral opening and bacteria are more likely to ascend into the female bladder because of the shorter urethral lenght [141,160]. The vast majority of urinary tract infections is monobacterial and caused by *E.coli* in 75-95% of uncomplicated cases [138,148,160-162]. *Klebsiella pneumoniae* are isolated in 10-12%, *Proteus mirabilis* in 7-9%, *Staphylococcus saprohyticus* in 5-15% of cases [162-164]. In 10-15% of symptomatic patients no uropathogen can be isolated from the urine sample [146].

There is a wider microbiological spectrum of uropathogens in complicated cases, with a higher frequency of antmicrobial resistance compared with acute uncomplicated urinary infections [159,165]. *E.coli* remains here the most frequent uropathogen, but it is isolated in

lower rates (40-60%). Other common Gram negative bacteria include *Klebsiella pneumoniae*, *Proteus mirabilis*, *Providencia stuartii*, *Morganella spp*., *Pseudomonas aeruginosa*, *Acinetobacter spp*. [165]. Gram positive bacteria include coagulase-negative staphylococci, *E.faecalis*, group B ß-hemolytic streptococci [165].

Candida species are also frequently isolated from complicated cases. In elderly patiens and patients with stuctural abnormalities or chronic urological devices the infection is more likely polymicrobial [157].

There is high incidence of symptomatic UTI necessitating antimicrobial therapy as well as increasing population of highly susceptible patients who require antimicrobials for UTI [140].

Acute uncomplicaterd cystitis accounts for substantial proportion of antibiotics prescribed in general practice [153]. 32% increase in use of antibiotics specifically used for UTI was observed in the primary care from 2007 to 2011 in the Netherlands [166], whereas from Italy a fourfold increase was reported within a three-year observational period [167]. Especially the consumption of fluoroquinole antibiotics increased [168].

Parallel with the overuse of certain groups of antibiotics, the resistance rate of uropathogens is increasing. In South Korea the resistance rates of *E.coli* increased from 15.2% in 2002 to 23.4% in 2006 that indicates the necessity of re-evaluation of the current guidelines for empirical therapy in acute urinary tract infections [169]. ESBL-producing *E. coli* and *K. pneumoniae* and other resistant Gram negatives are being isolated more frequently from outpatient samples [149].

In this work we focused on the epidemiological evaluation of acute urinary tract infections.

2.6. Clinical aspects of urinary tract infections

The manifestation of uncomplicated UTI is usually easy to recognize in adult patients. Lower tract symptoms result from uropathogens producing irritation of vesical and urethral mucosa [150].

The presence of the following symptoms are suggestive of lower tract urinary tract infection:

- painful urination

- frequent urination
- urgent urination
- haematuria (macroscopic/microscopic)
- suprapubic tenderness or pain [155,170-175].

If these symptoms are present without urethral discharge, the likelyhood of uncomplicated lower UTI is 90-95% [176]. The presence of fever, flank pain or tenderness, gastrointestinal symptoms associated with dysuria, urgency, frequency stongly suggest acute pyelonephritis [150,173].

Acute uncomplicated cystitis (AUC) is usually a mild, self-limiting infection that resolves in 20-50% of patients within one week. 50-70% of lower UTI cases resolve without treatment, but symptoms may persist for months [146,166,177]. Most symptoms last no more than 3 days. The urine dipstick test is a valuable tool for detecting UTI [137].

Diagnostically, a positive nitrit test and/or positive positive leucoesterase are indicators for UTI. However, when both tests are negative, the possibility of infection cannot be ruled out completely, but strongly predictive for the absence of UTI [150,151,175]. In uncomplicated cystitis the performance of urine culture is usually not recommended [126,140,164,178]. Urine culture and susceptibility testing is important at severe, recurrent and complicated infection, or when the diagnosis is unclear, eg. in the elderly patients [179]. In patients with recurrent cystitis, urine culture with antimicrobial susceptibility must always be performed and urological/gynecological evaluation is needed to exclude morphological and/or functional abnormalities [150,173].

Antibiotics are superior to placebo regarding clinical and microbiological cure in adult non-pregnant women with acute uncomplicated cystitis, however, they are associated with more adverse events [155].

Short-course therapy is preferred over longer courses of antibiotics [179]. 80-90% of patients are treated empirically, nitrofurantion, trimethoprim-sulfamethoxazole (co-trimoxazol), fluoroquinolones, beta-lactams are the most commonly used agents in the treatment of uncomplicated cystitis.

In complicated UTI the treatment should always be based on the urine culture results and susceptibility testing, moreover on the management of underlying condition [170,174,175,179,180].

The therapeutic regimens (first-, and second-line agents, alternatives) are usually summarized in clinical guidelines that are developed by national scientific committees. The application of certain antibiotics in the first-line treatment should be limited depending on the local resistance patterns of uropathogens.

Supplementary therapy in uncomplicated UTI includes good hydration, use of analgetics, use of cranberry products as adhesion blockers [138,148,166,181].

3. MAIN RESEARCH OBJECTIVES

3.1. National ambulatory antibiotic consumption study

- To analyse the pattern of the Hungarian ambulatory antibiotic consumption in acute cystitis in 2007
- To compare Hungarian antibiotic use in acute cystitis with the disease-specific quality indicators developed by ESAC
- To evaluate the rate of adherence to the available national antibacterial guidelines

3.2. Regional ambulatory patient-level antibiotic use survey

- To study patient characteritics (age, gender, symptoms, chronical underlying morbidities) in the Southern Great Plain region
- To assess outpatient antibiotic treatment of different urinary tract infections
- To estimate the rate of antibiotic overuse in acute cystitis

4. METHODS

4.1. General methods

All statistical analyses were performed with SPSS (version 22.0) and a *p* value less than 0.05 was considered as statistically significant. MS Excel, MS Access and the R programming language and environment (2.9.0) were also used during the data procession.

4.2. National ambulatory antibiotic consumption study

The crude data on systemic ambulatory antibiotic use were obtained from the *Hungarian National Health Fund Administration* for a *6-months period* (January – June 2007). The analysis focused on all prescriptions claimed in the community pharmacies of Hungary (n= 2010 pharmacies).

Antibiotic consumption was investigated by the Anatomical Therapeutic Chemical (ATC) classification and defined daily dose (DDD) measurement unit (version 2008). The drug utilization 90% (DU90%) segment of the antibiotics used in acute cystitis was also determined. Population data originated from Eurostat.

According to the 1/2003 (I.21.) ESZCSM ordinance of the Hungarian Ministry of Health the International Classification of Diseases (ICD) codes (version 10) must be displayed on Hungarian prescriptions that allowed the assessment of antibiotic use by indication, except for age and gender. The quality indicators developed by ESAC pertain to the U71 code of the International Classification of Primary Care, second revision (ICPC-2-R code). The conversion between the ICD-10 and the ICPC-2-R codes was performed by a computer programme of the Norwegian Centre for Informatics in Health and Social Care [182].

In the present analysis the ESAC-developed disease-specific quality indicators were used [70].

The **ESAC 3a indicator** represents adult female patients with cystitis (ICPC-2R: U71) receiving systemic antibacterial therapy (acceptable range: 80 – 100%).

The **ESAC 3b indicator** shows the percentage of 3a patients receiving the recommended antibacterials (ATC: J01EA: trimethoprim and derivatives, or J01XE: nitrofuran derivatives, or J01XX: other antibacterials; acceptable range 80 – 100%).

The **ESAC 3c indicator** reflects the percentage of 3a patients receiving fluoroquinolones (ATC: J01M: fluoroquinolones; acceptable range 0 – 5%). The ESAC 3b disease-specific quality indicator was estimated by the relative use of the ESAC recommended antibacterial agents and ESAC 3c by the relative use of quinolones in acute cystitis.

Originally ESAC recommended the use of the J01EA group antibiotics (trimethoprim and derivatives) for acute cystitis. This ATC group is not available in Hungary so we considered the use of the J01EE group (combination of sulfonamides and trimethoprim) instead of the J01EA group. The results were compared to the ESAC-predefined acceptable ranges.

In 2007 there were 3 different national clinical guidelines available for the treatment of acute cystitis:

1. the first was published by the **Hungarian Professional College of Infectious Diseases and Urology** [183],
2. the second was published by the **Hungarian Professional College of Internal Medicine and Nephrology** [184]**,**
3. the third by the **Editor of the Clinical Guide to Infectious Diseases Manual** [185].

All guidelines concerned adult, fertile female patients suffering from uncomplicated acute cystitis. Adherence to these guidelines was also calculated. Moreover, the form and content of the guidelines were assessed.

4.3. Regional ambulatory patient-level antibiotic use survey

A cross-sectional study was conducted between March and December, 2013. At a Regional Postgraduate Training Course for General Practitioners, out of 49 participants 25 GPs agreed to participate in our survey. Six GPs dropped out, 19 GPs completed the study (11 from urban, 2 from semi urban, 6 from rural practices). These practices cover a population of approximately 32 400 people (2.9 % of the regional population). The involved GPs represented 3% of all the GPs in the region [186]. Participation was voluntary and did not involve any financial incentives. A short oral presentation was held about the aims and methods of the study and participants received further written information.

Participating GPs were asked to fill in a registration sheet about each eligible patient. Registration sheet was designed by our research team and a GP representative. A pilot testing was performed to polish and correct questions if needed. Registration sheets were mailed and returned by post. The registration sheet contained data on presentation of symptoms, whether or not diagnostic measures were performed, patient characteristics including antibiotic allergy, presence of predisposing factors for UTI, details of prescribed medicines, suggested treatment and previous episodes of cystitis. Active participation of GPs were encouraged by regular telephone calls. Based on physician official registration numbers, data on GP characteristics (specialisation, years of practise) were retrieved from the national Health Registration and Training Center [187].

Eligible were all patients over the age of 16 years contacting their GP with suspected UTI or symptoms of UTI. Pregnant women and patients with complicated pyelonephritis were excluded as these patients were referred to secondary care. Patients with accompanying symptoms of genital problems (prostatitis, vaginal discharge) were also excluded.

Based on registered symptoms and co-morbidities UTIs were classified into 3 groups: acute uncomplicated cystitis, acute complicated cystitis and acute uncomplicated pyelonephritis. UTI was categorised uncomplicated if it occurred in otherwise healthy women and complicated if it occurred in men or in women with underlying conditions. The complicating factors were as follows: male gender, diabetes, renal failure, presence of an indwelling urethral catheter, stent, nephrostomy tube or urinary diversion, recent urinary tract instrumentation, functional or anatomic abnormality of the urinary tract (including obstructions), renal transplantation, immunosuppression. If patient had fever, flank pain/costovertebral angle tenderness or nausea/vomiting the UTI case was considered as pyelonephritis.

ATC classification of antibiotics were used (version 2015). The data analysis was carried out by using SPSS for Windows 22.0.

Possible determinants of fluoroquinolone prescribing practice in different categories of UTI (patient characteristics: age, recurrent infection, doctor characteristics: years of practice, specialty) were analysed by univariate analysis and classification tree. Short term courses were defined as single-dose administration of fosfomycin-tromethamol, 3-days of fluoroquinolone, 5-days of beta-lactam and 5-7 days of nitrofurantoin use.

The approved study design did not allow us conducting patient follow up (i.e. re-consultation, therapy failure/switch, results of urine culture). This study is intended to show

performed diagnostic measures and recommended/prescribed therapy following the first visit to GP with suspected UTI.

The study was approved by the Regional Human Medical Biology Research Ethical Board of the University of Szeged, Hungary (number: 203/2012). Informed consents were obtained from both GPs and individual patients, the anonymity of the patients was ensured during the whole investigation.

5. RESULTS

5.1. National ambulatory antibiotic consumption study

For the 8 ICD codes (N3000, N3010, N3020, N3030, N3040, N3080, N3090, and N3900) that corresponded to the U71 code of the ICPC-2-R code system, the recorded antibiotic use was 1.24 DDD per 1000 inhabitant-days, representing 6.9% of all antibacterial use in the Hungarian ambulatory care sector. The 3 dominating diagnoses were acute cystitis (N3000), urocystitis (N3090), and urinary tract infection, site not specifi ed (N3900), with a cumulative share of 94.2% within the studied indications (i.e., the 8 ICD codes belonging to the U71 code). In order to be able to compare our antibiotic use data to the national guidelines (which refer to acute cystitis cases), we focused all further calculations on the 2 dominating ICD codes that refer to acute cystitis cases: acute cystitis (N3000) and urocystitis (N3090). Antibiotics were administered orally. The 10 antibacterials with the highest use („top 10" agents) represented 90.4% of all systemic antibiotic use for acute cystitis. The adherence rate to different recommendations (i.e., ESAC and Hungarian guidelines) and the use of the top 10 agents are displayed in *Table 2*.

		Use in acute cystitis		Antibiotics recommended by the guidelines				
				National guidelines				
		DDD/1000 inhabitant-days	%	1	2	3	ESAC QI 3b (AR: 80-100%)	ESAC QI 3c (AR: 0-5%)
Total antibiotic consumption in cystitis		1.06	100 %					
Top 10 Antibiotics (90.41%)	1. Norfloxacin	0.28	25.94	x	x	x		NR
	2. Ciprofloxacin	0.20	18.96	x		x		NR
	3. SMX-TMP	0.15	14.34		x		**x**	
	4. Ofloxacin	0.09	8.45	x		x		NR
	5. Nitrofurantoin	0.07	6.75	x	x	x	**x**	
	6. Co- Amoxiclav	0.06	5.97		x	x		
	7. Cefuroxime	0.04	3.70		x	x		
	8. Fosfomycin	0.02	2.22	x			**x**	
	9. Doxycycline	0.02	2.19					
	10. Nalidixic acid	0.02	1.89					
Adherence to guidelines (%)				**63.27%**	**59.28%**	**74.17%**	**23.31%**	**56.22 %**

1: Guideline of the Hungarian Professional College of Infectious Diseases and Urology, **2**: Guideline of the Hungarian Professional College of Internal Medicine and Nephrology , **3**: Editorial Guideline of the Clinical Guide to Infectious Diseases Manual, **ESAC**: European Surveillance of Antimicrobial Consumption, **ESAC QI 3b** disease-specific quality indicator: relative use of recommended antibacterials, **ESAC QI 3c** disease-specific quality indicator: relative use of quinolones, **NR**: not recommended by ESAC, **AR**: acceptable range, **SMX-TMP:** Sulfamethoxazole and trimethoprim, **Co- Amoxiclav:** Amoxicillin and clavulanic acid

Table2. Relative use of the top ten antibacterials used in acute cystitis and their recommendation status in the different guidelines

Fluoroquinolones constituted 54.3% of the total antibiotic consumption, with three antimicrobials (norfloxacin, ciprofloxacin, and ofloxacin) among the top 10 agents (*Figure 3*).

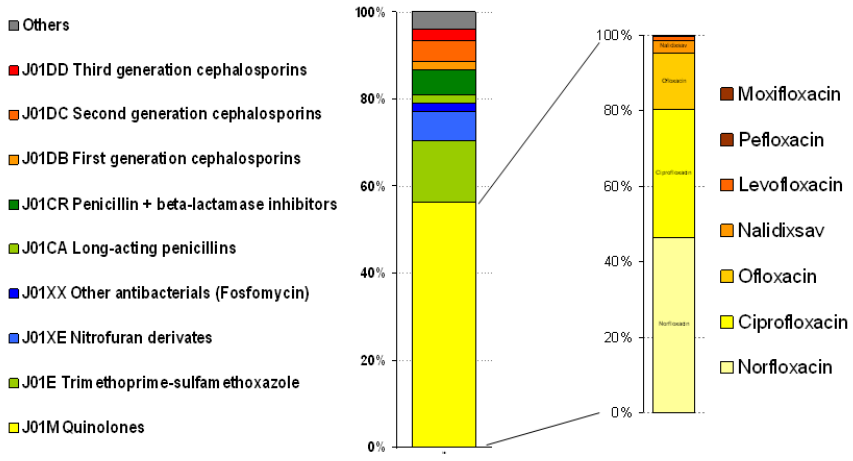
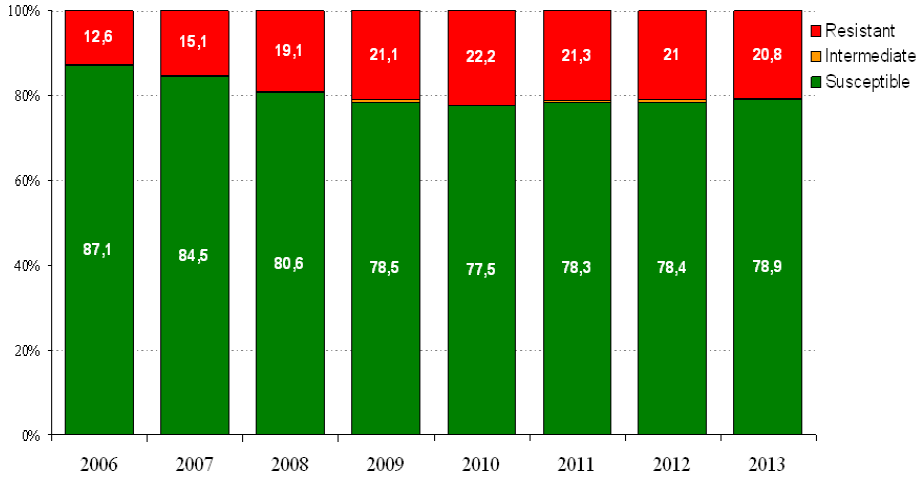


Figure 3. Distribution of the antibacterials used in acute cystitis and distribution of quinolones

The resistance rates of *E.coli* to ciprofloxacin increased substantially, from 11.6% in 2006 to 22.2% by 2010 in outpatient urine samples, although there was a slight decrease in the last two years *(Figure 3).*



Source: National Centre for Epidemiology, Hungary (2015)

Figure 4. Resistance rates of *E.coli* to ciprofloxacin in the primary care in Hungary, 2006-2013.

The proportion of beta-lactam use was 17.0% *(Table 2)*. Co-amoxiclav was the most frequently prescribed beta-lactam (share within the penicillin group: 70.3%), followed by ampicillin and amoxicillin.

Besides the most popular cephalosporin – cefuroxime (which covered 43.8% of cephalosporin use) – 3 other agents had notable use: cephalexin, cefixime, and ceftibuten. The

adherence rate to the 3 available Hungarian guidelines ranged between 59.3% and 74.2%. The relative consumption of antibacterials not among the recommended agents in any Hungarian guidelines was 7.8%. The use of antibacterials recommended by ESAC (quality indicator 3b) was far below the acceptable range, while the proportion of fluoroquinolones (quality indicator 3c) exceeded the ESAC recommended range more than 10 times *(Table 2)*.

During the comparison of the three guidelines some deficiencies and contradictions were also identified (*Table 3).*

	National guidelines		
	1	**2**	**3**
Separating complicated and uncomplicated cases	+	+	+
Marking the target patient population by gender	+	+	+
Marking the target patient population by age	+	+	-
Recommending non-pharmacological treatment (eg.cranberry products)	**0**	+	**0**
Recommending supplementary treatment (eg. analgetics)	+	**0**	**0**
Recommending urine dipstick examination	+	+	**0**
Displaying references	+	**0**	**0**
Duration of therapy shown	+	+	+
Recommendation and disclosure of evidence levels	+	**0**	**0**
Differentiation of first- and second-line agents	**0**	+	**0**
Flow diagram/table helping the therapeutical decision	+	+	+
Concordance between the figure/table and the text of the guideline	**0**	+	**NI**
Emphasizing antibiotic resistance	+	+	**0**

Abbreviations:

1: Guideline of the Hungarian Professional College of Infectious Diseases and Urology

2: Guideline of the Hungarian Professional College of Internal Medicine and Nephrology

3: Editorial Guideline of the Clinical Guide to Infectious Diseases Manual

+:yes; 0:no; NI: cannot be interpreted

Table 3. Comparison of the national guidelines for the treatment of acute cystitis

5.2. Regional ambulatory patient-level antibiotic use survey

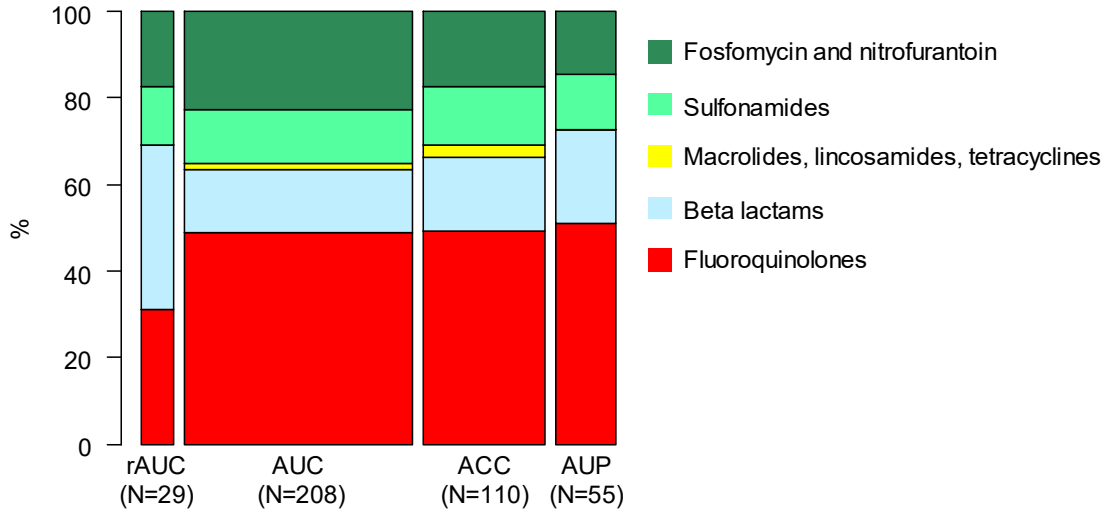
A total of 510 evaluable registration sheets were returned from the participating GPs. Due to ineligibility, 82 patients were excluded from further analysis. The median number of patients recruited per GP was 28 (range: 10-47). *Table 4* summarizes the patients' characteristics. The majority of patients were females with acute uncomplicated cystitis. Complicating factors were present in every fourth patient.

		N	%
Gender			
	male	30	**7.0**
	female	398	**93.0**
Age			
	mean±SD (min-max)	52.36± 20.21 (16-98)	
	65< years	132	**30.8**
UTI category			
	ACC	116	**27.1**
	AUC	256	**59.8**
	AUP	56	**13.1**
Recurrent			
	Yes	83	**19.4**
Presence of complicating factors			
	Yes	*104*	***24.3***
most frequent			
	diabetes	*37*	***8.6***
	incontinence	*34*	***7.9***
Beta lactam allergy			
	Yes	37	**8.6 %**

ACC: acute complicated cystitis
AUC: acute uncomplicated cystitis
AUP: acute uncomplicated pyelonephritis

Table 4. Patients' main characteristics

Patterns of antibiotic use is shown in *Figure 5*, while *Table 5* details patient management and the toplist of prescribed antibacterials.



rAUC: recurrent acute uncomplicated cystitis
nrACC: non-recurrent acute complicated cystitis
AUC: acute uncomplicated cystitis
AUP: acute uncomplicated pyelonephritis

Figure 5. Antibiotic use pattern by UTI type

Urine analysis was performed in almost every case, while midstream urine sample for urine culture was obtained in every fifth case of acute complicated cystitis (ACC) or acute uncomplicated pyelonephritis (AUP). Overall antibiotics were recommended in 402 cases (93.9 %), while analgesics were recommended to every tenth patient with UTI symptoms (Table 5). General practitioners' treatment practice differed considerably: antibiotics were prescribed for 60% -100% of their patients presenting with UTI symptoms. Overall nine out of the nineteen GPs recommended at least once analgesic use, which were recommended to 3.7 % - 100 % of their UTI patients, depending on the consideration of the individual GP.

Oral antibiotic monotherapies were prescribed exclusively. Beside the more frequent use of fosfomycin in uncomplicated cystitis, the pattern of antibiotic use was similar in the three main UTI categories and showed dominance of fluroquinolone use (Figure 5 and Table 5). Only the therapeutic pattern of acute recurrent cystitis (rAUC) was different: in these cases not fluoroquinolones but beta-lactams were prescribed more frequently. The relative use of fluoroquinolones ranged between 7.7 % and 87.5 %. Nitrofurantoin was used rarely (13 cases). Short term antibiotic therapy (see definition above) was prescribed only in one third of acute uncomplicated cystitis cases.

		AUC	ACC	AUP
gender	Male		30	
	Female	256	86	56
age	mean±SD	48.1±19.6	64.4±16.3	46.7±20.5
	65 +	57 (22.3%)	62 (53.4%)	13 (23.2%)
AB use	yes	237 (92.6%)	110 (94.8%)	55 (98.2%)
	top 5	ciprofloxacin: 55 (23.2%) fosfomycin: 48(20.3%) norfloxacin: 48 (20.3%) sumetrolim: 30 (12.7%) amoxiclav: 14 (5.9%)	ciprofloxacin: 30; (27.3%) norfloxacin: 22; (20%) sumetrolim: 15; (13.6%) fosfomycin: 13; (11.8%) cefuroxime: 9; (8.2%)	ciprofloxacin: 13; (23.6%) norfloxacin: 10; (18.2%) sumetrolim: 7; (12.7%) cefuroxime: 5; (9.1%) fosfomycin: 5; (9.1%)
Short course antibiotic prescribed %		76 (32.1%)	32 (29 %)	14 (25.5)
Analgesics recommended		20 (7.8%)	16 (13.8%)	7 (12.5%)
Urinanalysis performed		216 (84.3%)	100 (86.2 %)	49 (87.5 %)
Urine culture requested		39 (15.2 %)	25 (21.5 %)	12 (21.4 %)

AUC: acute uncomplicated cystitis
ACC: acute complicated cystitis
AUP: acute uncomplicated pyelonephritis

Table 5. Diagnostic and therapeutic measures in different UTI types

Determinants of fluoroquinolone prescribing: Both the univariate analysis (Chi-square: 62 % vs 37 % relative fluoroquinolone use, $p<0.001$) and the multivariate analysis (classification tree) revealed that patients below 40 years of age were prescribed significantly more fluoroquinolones compared to those aged over 40 years *(Figure 6)*.

In the other two UTI categories (complicated cystitis, uncomplicated pyelonephritis) none of the analysed covariables showed siginificant impact on fluoroquinolone prescribing.

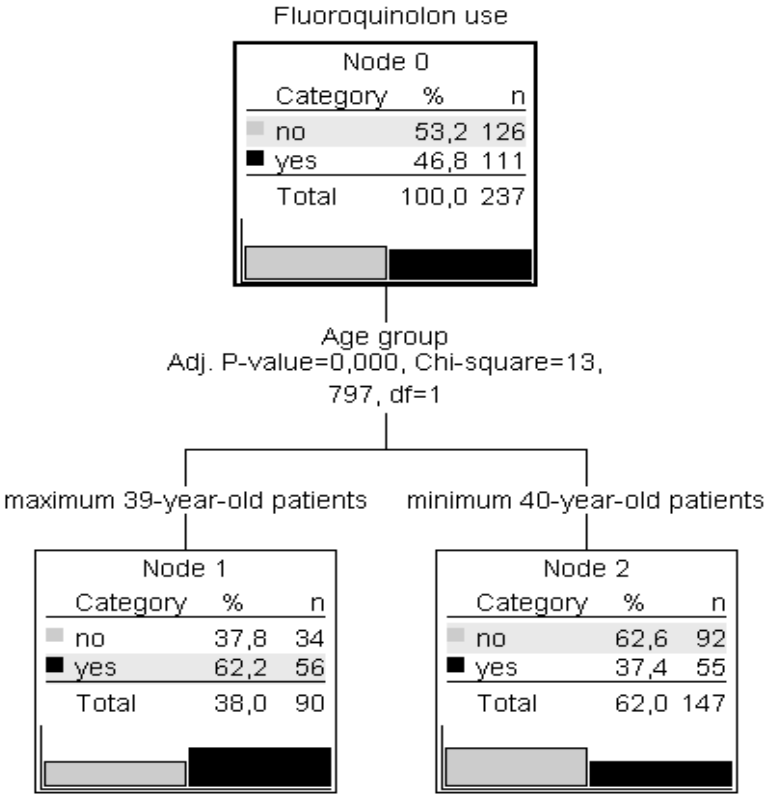


Figure 6. Classification tree of influencing factors of fluoroquinolone use in acute uncomplicated cystitis
(Analysed variables: patient's characteristics: age, recurrent infection, physician's characteristics: years of practise, specialty)

6. DISCUSSION

6.1. National ambulatory antibiotic consumption study

The results of the national antibiotic consumption study were well outside the acceptable ranges for the ESAC quality indicators, and national guidelines were followed in less than 75%.

Up to now, no published studies have used the disease-specific quality indicators developed by ESAC, which limited the comparison. The lack of similar studies may be due to the recent development of these indicators, but ″unknown″ indication can be the major obstructive factor. The Hungarian prescription database is valuable in the sense that drug prescription is linked to diagnosis; there is a lack of linkage between drug use and diagnosis in many national prescription databases including the Scandinavian ones [188]. The adherence rates to national guidelines for cystitis vary greatly in the literature.

In **Denmark and Norway** the adherence to national guidelines in primary care for UTI was the highest in Europe (94-100%) [87,189]. In **Finland**, the recommended first-line antibiotics (trimethoprim, pivmecillinam, or nitrofurantoin) were prescribed in 66 – 78% of cases at healthcare centres [190]. Dutch authors found that about 75% of the antibiotic prescriptions were for first-line agents (nitrofurantoin 32.7%, sulphonamides and trimethoprim 43.3%), others showed similar rate in Slovenia [57,128].

In our study we focused the analysis only on primary care, however, the type of the health care settings may influence the adherence to guidelines for empirical treatment of UTI. This statistically significant difference was showed in **Taiwan**, where the overall adherence rate for physicians was 72.1%, physicians in ambulatory care were less likely to adhere to UTI guidelines (69.5%) than physicians working in medical centres or regional hospitals (86.6% and 81.3%) [191]. On the other hand, in a **Spanish** study, only 17.7% of patients were treated empirically with the recommended first-choice antibiotics [126]. The general lack of adherence to national guidelines has also been demonstrated among American primary care physicians. Fluoroquinolones were given in 35.4% of cases, while first-line agents sulfamethoxazole – trimethoprim-sulfamethoxazole (TMP-SMX) and nitrofurantoin were prescribed in 29.8% and 18.8%, respectively [168].

Low guideline adherence rate was also reported from **France**, where in 71.4% of the cases the prescribed antibiotic was not the one recommended as first-line treatment, the 60% of UTI cases were treated with fluroquinolones, in 17.8% with nitrofurantoin and 6.5% with TMP-SMX. The prescriptions still adhered to the previous and out-of-date recommendations, while the resistance rates were increasing and exceeded 20% in the case of TMP-SMX [192].

In a recent **American** article investigating the concordance with the IDSA guidelines for uncomplicated UTI found that overall concordance (antibiotic type, dose, frequency, and duration) was 33.96%, 64% of patients were prescribed an antibiotic type concordant with the current IDSA guidelines [30].

Our survey showed that SMX – TMP and nitrofurantoin made up 13.8% and 6.9% of antibiotics for acute cystitis, respectively, **TMP-SMX** was the third most commonly utilized antibiotic in Hungary. The guideline of the Professional College of Internal Medicine and Nephrology suggested TMP-SMX for a 3-day treatment in UTI [184], but in the other two guidelines the role of this agent was not clearly interpreted. The guideline of the Hungarian Professional College of Infectious Diseases and Urology did not recommend empirically based on a smaller national case-study without any references in which the TMP-SMX resistance exceeded 21%.

In Israel, TMP-SMX was the most frequently used agent (25% of all cases), followed by nitrofurantoin (14.7%) [193]. TMP-SMX is the least expensive treatment option in UTI [159]. The current and former guidelines of the Infectious Diseases Society of America and European Society for Clinical Microbiology and Infectious Diseases also recommends that the administration of TMP-SMX should be avoided if resistance prevalence is known to exceed 20% [194,195].

Due to the lack of proper Hungarian TMP-SMX resistance data in 2007, the appropriateness of empirical TMP-SMX use cannot be evaluated retrospectively. However, the degree of difference of the recommended agents from the international quality indicators was high (23.3% vs the ideal 80-100% or 37.6% vs 80-100%), even if we presume that the application of TMP-SMX did not have any grounds in Hungary. National TMP-SMX resistance data of *E.coli* strains isolated from urine samples are available since 2008 in Hungary. The inpatient and outpatient resistance data have been published separately since 2010 [196].

Olson et al reported that 29.6% of *E.coli* strains isolated from uncomplicated young female patients were resistant to TMP-SMX, and ciprofloxacin resistance was 11.8% [197]. Frequent use of TMP-SMX (22% of cases) and quinolones (78% of patients) for outpatients were

described by Swiss authors suggesting that current guidelines are not often followed. The concerned physicians were predominantly (70%) general practitioners [198]. In Germany 61% of primary care physicians prescribed TMP-SMX empirically to treat uncomplicated UTI, which was not adherent to the national guideline [199]. Despite increasing tendency of trimethoprim/TMP-SMX resistance in Canada or in some regions of the USA, this agent can still remain the first-choice empirical therapy of uncomplicated UTI [136,164]. At a resistance prevalence of 20%, the estimated clinical cure rate is 88%, the bacteriological one is 84%. Clinical failure may occur in 40-50% of women treated with TMP/SMX if uropathogen is resistant [200].

Gastrointestinal side-effects (3-8%), rarely hypersensitivity skin reactions (1.6-8%), hematologic reactions (neutropenia/agranulocytosis) and nephrotoxicity (more commonly in patients with preexisting renal disease) may also limit their administration beyond the high local resistance [136,181,201,202].

Concerns about increased TMP-SMX resistance have contributed to greater use of quinolones worldwide, but widespread use of quinolones might also promote resistance to these agents [136]. In Hungary quinolones were utilized in 60% for the treatment of UTI, whereas in Turkey this was only 26% [203]. **Ciprofloxacin**, the most commonly prescribed fluoroquinolone in our study has a good tissue penetration and high potency (two to four-fold higher than norfloxacin against Gram negative pathogens) the most common Gram negative bacteria including uropathogens (*E.coli*, *Klebsiella*, *Enterobacter*, *Proteus* species). Increasing use over the last two decades has been associated with increased resistance [204-206].

In Germany and the USA, fluoroquinolones were prescribed in a third of cases and an increase in *Escherichia coli* resistance to ciprofloxacin from 7.7% to 14.5% was detected during a 3-year-period [168,207]. In South Korea the resistance rates of *E.coli* isolated from acute uncomplicated cystitis to ciprofloxacin increased from 15.2% in 2002 to 23.4% in 2006, indicating the re-evaluation of the guidelines for empirical therapy [169]. Between 1998 and 2005 levofloxacin use increased from 3.1 to 12.7 prescriptions per 1000 visits and resistance increased as well, from 1% to 9% in outpatients [208].

Particularly heavy fluoroquinolone prescription rates were reported from Italy (65% of prescriptions), Spain (73%), Portugal (61%), France (57%), Switzerland (64%) and Belgium (63%) [209]. The fluoroquinolones were the most commonly prescribed agents in uncomplicated urinary tract infections in latvian general practices [155].

The long term harmful effects of quinolone overuse are the increasing resistance of uropathogens due to selective antimicrobial pressure and the increasing occurrence of *Clostridium difficile* infection. Exposure to quinolones and cephalosporins were found to be a significant independent risk factor for *C. difficile*-associated diarrhoea [210,211].

Fluoroquinolone resistance is increasing worldwide, though the rates have not been as high as those for TMP-SMX [169]. Overuse of broad-spectrum agents like the fluoroquinolones might promote resistance that will affect negatively not only the treatment of uncomplicated UTI but also other serious systemic infections [136]. Quinolones should be used as first-line agents only in complicated UTI and in uncomplicated cases where there is allergy to the first-line agents.

Implementation of updated guidelines may have a favourable effects on the consumption of quinolones. In France a 13.2% decrease was noticed in the prescription of norfloxacin after introduction of a new regional guideline [212].

In Hungary, the use of quinolones dominated in acute cystitis. As a consequence of quinolone overuse and misuse in the primary care, the resistance rate of *E.coli* increased from 14.6% in 2006 to 21.3% by 2011 (European Antimicrobial Resistance Surveillance Network reported that the fluoroquinolone resistance of *E.coli* isolated from invasive samples reached 20% in 2005) [196,213]. As 2 out of the 3 Hungarian UTI guideline recommended the fluoroquinolone class as first-line treatment in acute noncomplicated cystitis in 2007, they could be responsible for the massive fluoroquinolone use and the increase in fluoroquinolone resistance.

The guideline of European Association of Urology, the IDSA guideline and German national guideline on the treatment of uncomplicated urinary tract infection equally recommend quinolones only as alternative agents due to the increasing resistance and TMP-SMX in areas with known resistance rates for *E.coli* under 20% [151,194,214].

In Canada quinolones are also considered as a second-line choice treatment, because of their cost and potential for development of resistance [136]. However, in Japan a 3 days of therapy with fluoroquinolones or 7 days with beta-lactams is still recommended for empirical therapy, remarking that these regimens should be re-evaluated in the next decade [169,215,216]. The consumption rate of internationally preferred agents, nitrofurantoin and fosfomycin were considerably low in Hungary.

Nitrofurantoin has been used in the therapy of UTI for more than 50 years worldwide, whereas the fosfomycin for 30 years. Nitrofurantoin and fosfomycin-trometamol have excellent in vitro antimicrobial effects, and preserved their activity against the most common

uropathogens despite the increasing antibiotic resistance [148,217-220]. In Hungary the susceptibility rate of *E.coli* strains to nitrofurantoin was 96.1% in 2012, and no recent data were published regarding the national resistance rate of fosfomycin [196].

The low prescription rate of nitrofurantoin use could be explained in part by its gastric and pulmonary adverse effects, which are noted in the guidelines published by the Hungarian Professional College of Urology. Moreover, its low eradication rate was also mentioned. Secondly, permanent supply problems might impede the use of nitrofurantoin.

Nitrofurantoin was prescribed as often as quionolones in Canada, whereas the prescription rate of fosfomycin was only 1.9% in Canada [31]. Nitrofurantion is bacteriostatic in low doses, bactericide in high doses, was found also effective in the treatment of extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli*-related lower urinary tract infection [221]. Administration of nitrofurantoin may contribute to a reduction in overall quinolone use and thus help to reduce selection pressure for increased fluroquinolone resistance [222]. It must be noted that nitrofurantoin has a poor activity against *Proteus spp*. *Serratia spp*., *Pseudomonas spp*., and should not be used to treat UTI caused by these organisms [223-225]. It is also restricted to use in pregnancy and renal impairment [226].

The resistance figures of nitrofurantoin among uropathogens remain low (under 10%, on average 1-2% worldwide, and 4.5% in Hungary) [222,227-231] and became an important treatment option for uncomplicated UTI in the era of increasing fluoroquinolon and TMP-SMX resistance [222]. In his study *Naber* described high prescription rate of nitrofurantoin in the Netherlands (27% of prescriptions), Finland (18%) and Canada (21%) in uncomplicated UTI. Fosfomycin was commonly used in Italy (18%) and France (16%) [209]. The application of nitrofurantoin was cost minimizing when the fluoroquinolone resistance exceeded 12% and TMP-SMX resistance exceeded 17%.

Since 1988 **fosfomycin-trometamol (FMT)** has been extensively used in several European countries for single dose therapy in uncomplicated urinary tract infections [218,220]. After many years of use, fosfomycin-trometamol continues to be active against the most common uropathogens. *Konkoly-Thege* investigated the in vitro effectiveness of fosfomycin trometamol and nine other antibiotics for uropathogens isolated from lower UTI and described a very high rate of susceptible *E.coli* strains (97.5%) to FMT in 2000. The *E.coli* isolates were susceptible to nitrofurantoin in 96.2% and to TMP-SMX in 70.7% [232].

This survey result supports the fact that FMT and nitrofurantoin could have been introduced much earlier as a first-line agent in Hungarian UTI guidelines - and TMP-SMX

should have been ranked to the second-line agents - but as our survey proved they had a marginal role in the antibiotic consumption for uncomplicated UTI.

Nowadays ESBL-producing strains are appearing and causing uncomplicated UTI more frequently in outpatient settings among previously healthy individuals [149,216,233].

In a Greek publication more than 90% of the *Enterobacteriaceae* isolates were found to be susceptible to fosfomycin. In 93.8% of patients fosfomycin-trometamol was clinically effective against uncomplicated or complicated UTIs that were caused by ESBL-producing *E.coli* [224]. In other studies the resistance rate of ESBL-positive *E.coli* to fosfomycin was 0.3%-3%, whereas to *K.pneumoniae* it was 7.2%. Cross resistance with other classes of antimicrobial agents is rare [225,226,231].

The marginal role of fosfomycin in the treatment of acute cystitis in Hungary is not surprising, as it is recommended only by the guideline of the Hungarian Professional College of Urology [184]. A single dose of fosfomycin-trometamol was equally effective to amoxicillin-clavulanic acid for 5-7 days in patients with susceptible uropathogens [224]. The clinical remission rate and bacteriological eradication rate in patients treated with FMT was 83%, whereas with ciprofloxaxin 81% and 78%, respectively [234]. Short-course regimens improve compliance, the cost of therapy and the frequency of adverse reactions are lower in the individual patient, and there are less collateral effects on the environmental flora [229]. Fosfomycin as a bactericidial antibiotic acts as a cell wall inhibitor by interfering the first step in peptidoglycan biosynthesis [225].

Its appropriate antimicrobial spectrum, tolerability, safety, clinical efficacy and excellent resistance profile, lack of cross-resistance support the choice of the national guidelines to include fosfomycin as an ideal first-line therapeutic option in the therapy of uncomplicated cystitis in the primary care [218,223,231,235]. The fosfomycin is more expensive than nitrofurantioin and TMP-SMX [223].

Beta-lactams should also be considered in the therapy of uncomplicated cystitis in primary care, but there are country specific differences [229]. Beta-lactams (amoxicillin-clavulanic acid, cefdinir, cefutroxim, cefaclor, cefpodoxime-proxetil) are recommended as alternative antibiotics in uncomplicated cystits by the current UTI guideline of IDSA and the German National Guideline [151,194,199].

A local guideline of the Michigan University also mentions cephalosporins as second-line agents [164]. Their effectiveness was found equal to TMP-SMX in short-term as well as in long-term treatment [236,237].

However, cephalosporins may yield increased incidences of recurrences and of adverse events (particularly vaginitis) more common than trimethoprim or TMP-SMX, they continue to play a role in the management in pregnant women with UTI [144,147].

Beta-lactams are less effective in clearing Gram-negative rods from the vaginal and colonic flora, they are rapidly excreted in urine, thus may predispose to recurrence [195,238]. administered cephalosporins (cefpodoxime, cefprozil, ceftibuten) result in moderate decrease in number of Enterobacteriaceae and significant colonization with *Clostridium difficile* [239].

Cefpodoxime demonstrated significantly poorer activity the ciprofloxacin in eradicating *E. coli* from the vaginal flora in the study of *Hooton et al*. [240] Generally, beta-lactams have inferior efficacy and more side effects compared with other UTI antimicrobials, therefore a cautious administration is suggested. Ampicillin and amoxicillin are no more recommended for empirical treatment as very high prevalence of antimicrobial resistance to these agent is reported worldwide [194,214]. Cephalosporins are often not effective against ESBL-producing bacteria [225]. Since 2014 the European Association of Urology does not suggest cefpodoxime-proxetil as an alternative agent [214].

In our study the consumption of beta-lactams was relatively low, the most frequently prescribed agents were amoxicillin-clavulanic acid (5.97%) and cefuroxim (3.7%). Similar beta-lactam consumption rate was found in Austria, meanwhile in Greece it was 24%, in UK 19% [209]. In Singapore amoxicillin-clavulanic acid was the first choice in empirical treatment in UTI because of high uropathogen resistance quinolones and cotrimoxazol [241].

Kim et al suggested that amoxicillin-clavulanic acid, cefaclor and cefpodoxime-proxetil are appropriate choices in 3-7 days regimens in the USA only in cases when first-line agents are contraindicated (local antimicrobial resistance or patient allergy) [30]. In Malaysia prescription of cephalosporins (13.3%) dominated over quinolones and the local antibiotic guidelines recommend cefuroxime as an alternative antimicrobial [242].

The three Hungarian UTI guidelines were not equally considering beta-lactams:

- the **editorial guideline** recommended second and third generation oral cephalosporins for a 5-day therapy, excluding the first generation cephalosporins empirically due to their higher resistance rates [185],
- the **internal medicine guideline** suggested clavulanic acid/sulbactam aminopenicillines and first generation cephalosporins in the emiprical treatment of acute cystitis [184],
- the **infectology and urology guideline** did not recommend any beta-lactam in the tables, only in the text they suggested 5-day use of beta-lactams without further details [183].

Pivmecillinam, a beta-lactam and a prodrug of mecillinam, has been used for the treatment of acute uncomplicated cystits for more than 20 years. 45% of the drug is excreted in the urine and has high activity against uropathogens, particularly *E.coli* and other *Enterobacteriaceae*, although it is not very active against Gram positive cocci, cure rates of *S. saprohyticus* infection were 73-89% [243-245].

Pivmecillinam may spare the use of other agents such as TMP/SMX and fluoroquinolones where there are concerns about *E.coli* resistance in the community. Given twice daily for 7 days is found as effective as a 3-day fluoroquinolone therapy, with a 90% of microbiological cure rate after 3 days, 3x 300 mg dose [246]. Short treatment with pivmecillinam results in clinical and bacteriological cure rates similar to those obtained with other UTI antimicrobials [243]. Favourable resistance levels may promote its wider use throughout Europe and worldwide [153]. Its safety is confirmed in pregnant women, pivmecillinam has only a minor impact on the oropharyngeal, intestinal and skin microflora. 20-30% of prescriptions for acute cystitis in Denmark, Sweden, Norway are for pivmecillinam. In Finland 10% of acute uncomplicated cystits cases were treated with pivmecillinam [243,247]. Pivmecilliam is not marketed in many EU countries, although its resistance rates are low worldwide and 400 mg for 3 days can be considered the first drug of choice in many countries (Scandinavia, Netherlands, Austria, Canada) [214,229].

Many guidelines endorse this agent in the first-line regimen in the treatment of uncomplicated UTI. In Sweden for lower urinary tract infections a quite close adherence to current guidelines was demonstrated and there was a significant change in choice of prescribed antibiotics with an increase of pivmecillinam and nitrofurantoin and a decrease for trimethoprim between 2000 and 2005 [248].

The favourable resistance patterns of beta-lactams (cefuroxim 6.7%, cefixim 6.7%, cefotaxim 7.3% in 2013) according to the National Centre for Epidemiology possibly could allow their application as alternatives in the treatment of uncomplicated UTI in Hungary [196].

In summary, for substances like fosfomycin, nitrofurantoin or mecillinam „collateral damage" has not been documented or only to a lesser degree, they preserved their in vitro activity. Therefore, for empiric therapy of frequent uncomplicated cystitis **fosfomycin-trometamol**, **nitrofurantoin** or **pivmecillinam** (not listed in the USA and many European countries including Hungary) may represent good options as first-line antibiotics [149,151,214,249,250].

There are some limitations to this study. The ESAC quality indicators for cystitis were defined for female patients older than 18 years. Unfortunately we could not screen our data for sex and age, but this does not affect our results and conclusions as studies show that most acute cystitis cases occur in females of reproductive age [251].

Secondly, the Hungarian guidelines divide lower urinary tract infections into complicated and uncomplicated groups, while the ICD codes do not differentiate between these groups. As some of the agents that are recommended in the national guidelines for acute uncomplicated cystitis are not optimal for complicated cystitis (e.g., fosfomycin), the calculated adherence rates to Hungarian guidelines are slightly overestimated.

Thirdly, the ESAC quality indicators were defined for patients who should receive the recommended antibacterial agent. Unfortunately individual patient data were not available to us, only data on antibiotic consumption linked to an indication. As the prescribed DDD quantity of the different antibacterial agents used in acute cystitis did not differ considerably, the percentage of patients treated and the relative use of prescribed antibiotics is comparable.

6.2. Regional ambulatory patient-level antibiotic use survey

Despite the huge number of presentation of UTI cases in primary care and the possible ecological effects of related antibiotic prescribing, the number of recent studies focusing on evaluation of UTI treatment in general practices is scarce. In this work we intended to analyse antibiotic use pattern in different UTI types and analyse possible determinants of

fluoroquinolone choice. Our main finding was that antibiotic prescribing pattern was irrespective of the presence of complicating factors or anatomical localisation [214].

6.2.1. Proportion of patients treated with antibiotics

In comparable studies [126,180,252] patients with UTI were prescribed antibiotics in similar rate (~90% or above). As metanalysises showed that antibiotics are superior to placebo even in uncomplicated cystitis [70,155], the use of antibiotics seems to be justified in all types of UTIs except asymptomatic bacteriuria. This is in line with the UTI-related disease specific quality indicator which defines 80% or above the optimal range of antibacterial use in adult female UTI patients [70].

However a study conducted in the UK focusing only on uncomplicated urinary tract infection [253] found that empirical antibiotic treatment was initiated only in 61 % of patients compared to our higher rate of 94 % in this patient group. This difference can be explained by the fact that despite the European guideline where antibiotic treatment is recommended for all kinds of UTIs, the UK guideline on antibiotic prescription advises treatment should be delayed in uncomplicated cystitis of non-pregnant women to see if symptoms will resolve without treatment [254]. Another study on uncomplicated UTI also confirmed that antibiotic use can be substantially reduced by simply asking the patient about the willingness of delaying initiation of antibacterial agent [255].

6.2.2. Recommendation of analgesics

Symptomatic relief offered by pain killers are increasingly recognized as important in treatment of UTI however advocated by only a few guidelines [254]. Analgesics were given to minority of patients in this study which is not surprising as neither the European guideline [214], nor the valid national guideline (2010) discuss this therapeutic opportunity in UTI. As other studies focused on antibiotic treatment exclusively, comparison of analgesic use is not possible.

6.2.3. Diagnosis

Urine dipstick was requested in majority of cases similar to the **Spanish** UTI study [252]. As detection of pyuria is generally accepted as confirmation measure of UTI and may guide antibiotic choice (i.e nitrite test positive if *Enterobacteriaceae* is present), its use can be justified in all cases. At first sight, the request of midstream urine sample in uncomplicated cystitis might seem unnecessary, but it was ordered in 85 % in reccurent cases where urine culture is required for confirmation of diagnosis [214]. In complicated cystitis and in pyelonephritis investigation of urine culture is mandatory in all cases [214]. The recorded low rate of urine culture request in these latter cases can be explained by difficulties of the sample transport and the long turnover time of laboratory results [256].

6.2.4. Fluoroquinolone use

Usage of fluoroquinolones dominated in all UTI types in this study. Common ambulatory use of fluoroquinolones in treatment of UTIs has been reported from other European studies as well [192,257,252]. However low rate of fluoroquinolone use (6%) in this disease has been reported from **Norway** [189].

In more than 40% of uncomplicated cystitis cases fluoroquinolone use was initiated. This finding is similar to findings of **Spanish** [252], **French** [192], and **Latvian** authors [257], who recorded fluoroquinolone use in 46.6 %, over 60%, and 41% of these cases, respectively. The high rate of fluoroquinolone use in uncomplicated cystitis is not surprising in Hungary given the fact that their use has been proposed as first line treatment in the presently still valid national UTI guidelines [183,184].

Analysis of prescriptions for fluoroquinolones showed that doctors prescribed relatively less fluoroquinolones in patients over 40 years with uncomplicated cystitis. This finding may be explained by the fact that this is an easily curable type of UTI, while fluoroquinolone side effects and their potential to give drug interactions are more likely to happen with increasing age and in the presence of underlying co-morbidities [258,259].

Fluoroquinolones are considered as critically important antibiotics according to the WHO classification [260] and one of the antibiotic group that should receive highest priority for developing risk management strategy options (e.g. restricted use) to preserve their effectiveness in the future. Extensive fluoroquinolone use is major concern due to the high and increasing prevalence of resistant *E. coli* strains [261]. In several countries including Hungary fluoroquinolone resistance of *E. coli* exceeds 20% in non-invasive ambulatory samples [262], therefore their use in empirical treatment of UTI should be re-evaluated.

6.2.5. Other antibacterials

Fosfomycin was prescribed for more than 20% of patients with uncomplicated cystitis which is still considered as suboptimal. On the other hand the use of fosfomycin in complicated cystitis/pyelonephritis is not satisfactory due to the lack of activity against Gram-negative pathogens other than *E. coli* [263], therefore the recorded fosfomycin use should be regarded inappropriate in these cases. The low perscription rate for **nitrofurantoin** in uncomplicated cystitis was not surprising as national guideline emphasize its low eradication rate [183]. As a consequence many pharmacies would not stock them, resulting limited availability. A logical reason was not found for the few cases where macrolides, lincosamides or tetracyclines were prescribed, as these have no indication in UTIs at all [263].

6.2.6. Beta-lactams

For uncomplicated cystitis the European guideline only recommends **pivmecillinam**, which is not available in Hungary [214]. Hungarian national guidelines recommend **co-amoxiclav** as first line treatment which explains their widespread use in uncomplicated cystitis. Cefuroxim, which was amongst the top 5 agents in the initial empirical therapy for complicated cystitis and uncomplicated pyelonephritis however is not generally recommended as first line empirical treatment for these conditions due to the lower efficacy compared to fluoroquinolones [183,184,214]. The higher relative use of beta-lactams in recurrent cystitis could be explained by the fact that GPs who prescribed fluoroquinolones for the previous episode decided to switch antibiotic group due to the recurrence of infection.

6.2.7. Sulphonamides

Trimethoprim-sulfamethoxazol was prescribed as initial empirical treatment in 10 % in each UTI group. Their use as first line antibacterial therapy is recommended only in uncomplicated cystitis and only if resistance data is below 20% [183,214]. National sulfomethoxazol-trimethoprim resistance rate for *E.coli* (from ambulatory care urine samples) exceeds 20% [262], but given the fact that national resistance surveillance data often overestimate real resistance rates [264,265], the empirical use of TMP-SMX for uncomplicated cystitis - at least partly - can also be considered appropriate.

6.2.8. Antibiotic therapy duration

Short term antibiotic course was ordered to only every third patient with uncomplicated cystitis. Too long courses for uncomplicated cystitis have been reported from other studies as well [16,192] which can - at least partly – be explained by the lack of suitable packages for short term antibiotic courses [266]. In Hungary –with the exception of fosfomycin - the available antibacterial packages used in UTIs (fluoroquinolones, beta-lactams) are not designed for short-term courses and current reimbursement policy does not allow splitting marketed packs of medications. Moreover, indicating therapy duration is not a compulsory element of any drug prescriptions, all which suggests to GPs that antibiotic course duration should be tailored to the individual case.

6.2.9. Strength and limitations

Although many other studies are limited by the fact that individual GPs established the diagnoses [253,258,259] the study design enabled us to have a common diagnostic criteria. This allowed us to set up groups by classification furthermore we excluded misclassifying cases to justify broad spectra antibiotic use.

Only half of the invited GPs agreed to participate and further 6 GPs dropped out during the study. One of the main reasons for refusing participation was obviously the lack of interest and lack of time, however registration sheets could have been filled out within few minutes. Participating GPs may have been more motivated and interested in proper antibiotic prescribing practice. Prospective study design could also have further influenced prescribing habits, which can bias our results towards better outcome.

7. SUMMARY

In my PhD thesis I set out to demonstrate the outpatient antibiotic use pattern in cystitis in Hungary.

By using different data source and methods I intended to present antibiotic consumption data on indications, patient characteristics and provide insight into the everyday treatment practice in primary care settings, and to show the antibiotic misuse in the treatment of cystitis. I also aimed to highlight the current situation when there are still three different national guidelines available in the treatment of UTI and the prescribing habits found in this work may also be explained by this fact.

My main findings and suggestions are as follows:

- According to quality indicators the use of antibacterials recommended by ESAC in UTI was far below (23.3%) the acceptable range (80-100%).

- The research explored excessive use of fluoroquinolones for acute cystitis in Hungary. However, the pattern of use (i.e., the dominant fluoroquinolone use) was consistent with the national guidelines that were, and still are, in force. These guidelines are in contrast to the ESAC proposed acceptable range of 0-5% for fluoroquinolone use that was deemed relevant by an expert panel.

- The overuse of fluoroquinolones as first line agents may lead to the increase of fluroquinolone resistance. As the fluroquinolone resistance of *E.coli* exceeds 20% in non-invasive ambulatory samples in Hungary, its role in empirical treatment of UTI should be reconsidered.

- As consumption and prescription data show trimethoprim-sulfamethoxazole is still one of the favourized first-line agents in the empirical therapy of UTI in spite of the national resistance rates exceeding 20%.

- The suboptimal use of fosfomycin and nitrofurantion was found although these antibiotics are preferred internationally in the empirical therapy of UTI and low national resistance rates would allow their wider usage.

- Similar antibiotic use pattern in the treatment of all types of UTI patients have been recorded, despite the different antibiotic recommendations for the empirical first line treatment of different UTIs (complicated, uncomplicated, recurrent) in the primary care.

- The introduction of newer beta-lactams (eg. pivmecillinam, which is not yet marketed in Hungary) should also be considered as alternative agents in the empirical outpatient treatment of UTI as it has a favourable resistance profile.

- Further qualitative studies (eg. focus-groups) are needed to better understand the background of the antibiotic prescribing behaviour of the family physicians in the treatment of urinary tract infections in Hungary.

Patient safety and quality must be stand in the centre of XXI. century's health care systems. One of the most important pillar of patient safety is the optimal and prudent use of antibiotics preventing the spread of resistant bacteria and associated morbidities, and not least to be cost-effective.

There still appears to find considerable room to improve quality of antibiotic prescribing practice of GPs treating patients with UTI. Development of updated, user friendly guides on the diagnosis and treatment of UTI, raising of GPs awareness of their role in fighting antibiotic resistance and regular monitoring of their prescribing habits are needed in the future.

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APPENDIX

ORVOSI ADATLAP

1. Dátum: 20__év__hó__nap

2. Beteg életkora: *3. A beteg neme*: ☐ Férfi ☐ Nő

4. Milyen tünetek miatt jelentkezik a beteg? Kérjük X-el jelezze a fennálló panaszokat!

Dysuria ☐ Pollakisuria ☐ Csípő vizelet ☐ Haematuria ☐

Láz ☐ Suprapubikus/kismedencei fájdalom ☐ Lumbális fájdalom ☐

Hányinger ☐ Hányás ☐ Hasmenés ☐ Görcsös hasi fájdalom ☐

Húgycső váladékozás ☐

Egyéb: _____

5. Felállított diagnózis (BNO):

6. Történt-e vizelet rutinvizsgálat? IGEN ☐ NEM ☐

7. Vizelettenyésztés történt-e? IGEN ☐ NEM ☐

8. Ha történt vizelettenyésztés, annak eredménye:

9. Javasolt-e antibiotikumot a betegnek? IGEN NEM

*10. Amennyiben IGEN, melyiket?*_____

*11. Terápia javasolt időtartama:____nap, dózisa*_____

12. Antibiotikum allergia szerepel-e az anamnézisben? IGEN☐ NEM ☐

*13. Ha igen, melyik antibiotikum(ok)ra:*_____

*14. Milyen egyéb készítményeket javasolt?*_____

*15. Egyéb tanácsok:*_____

_____

16. Milyen húgyúti fertőzés kialakulására hajlamosító állapot/betegség ismert a betegnél? ***Kérjük X-el jelezze!***

Húgyúti daganat ☐ veseelégtelenség ☐ diabetes ☐ nephrolithiasis ☐

immunsupprimált állapot ☐ benignus prostata hyperplasia ☐

congenitális anatómiai rendellenesség ☐ vesetranszplantáció ☐

terhesség ☐ műszeres/műtéti beavatkozás a húgyutakban ☐

cystokele ☐ prolapsus uteri ☐ tartós húgyúti katéter viselése ☐

NINCS hajlamosító tényező ☐ Inkontinencia (betétviselés) ☐

Egyéb: _____

17. Az elmúlt féléven belül ***legalább kettő****, vagy egy éven belül* ***legalább három*** *húgyúti fertőzése volt-e a betegnek? (rekurrens húgyúti infekció)* ☐ IGEN ☐ NEM

Publication related to the Thesis

I.

Scandinavian Journal of Infectious Diseases, 2013; 45: 612–615

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healthcare

ORIGINAL ARTICLE

Treatment of acute cystitis in Hungary: comparison with national guidelines and with disease-specific quality indicators

ZOLTAN JUHASZ[1], RIA BENKO[2], MARIA MATUZ[2], REKA VIOLA[2], GYONGYVER SOOS[2] & EDIT HAJDU[1]

From the [1]Division of Infectious Diseases, First Department of Internal Medicine, Faculty of Medicine, and [2]Department of Clinical Pharmacy, Faculty of Pharmacy, University of Szeged, Szeged, Hungary

Abstract

Background: The aim of this study was to compare Hungarian antibiotic use in acute cystitis with the internationally developed disease-specific quality indicators and with the national guidelines. *Methods:* The aggregated national-level data on systemic antibiotic use was purchased from the National Health Fund Administration. The study period was January–June 2007. Antibiotic use in acute cystitis was evaluated by means of the defined daily dose (DDD) methodology. Quality indicators of antibiotic prescribing proposed by the European Surveillance of Antimicrobial Consumption (ESAC) team were the usage rate of recommended antibacterials and the usage rate of quinolones. Adherence to the available national guidelines was determined. *Results:* For acute cystitis, 1.06 DDD per 1000 inhabitant-days antibiotic use was recorded. The ESAC recommended antibiotic use in cystitis (23.3%) was well below the recommended range (80–100%). The consumption of fluoroquinolones was 56.2%, which exceeded the recommended range (0–5%) more than 10 times. The adherence rate to the Hungarian guidelines ranged between 59.3% and 74.2%. *Conclusions:* As both investigated disease-specific quality indicators were well outside the acceptable ranges, some inappropriateness of antibiotic use in cystitis seems to be present. Adherence rates to the different national guidelines were also moderate, but due to the general recommendation of quinolones, values should be interpreted with caution. New transparent guidelines – issued by the Hungarian Society of Family Physicians – should be introduced in Hungary, recommending quinolones only for second-line therapy.

Keywords: *Cystitis, antibiotic use, quality indicators, adherence to national guidelines, Hungary*

Introduction

There is much evidence to show that the inappropriate use of antibiotics increases resistance to these agents [1]. European Surveillance of Antimicrobial Consumption (ESAC) data show that Hungary ranks in the middle of European countries with regard to the use of ambulatory antibiotics [2]. However, up-to-date information on the quality of antibiotic consumption in the ambulatory care sector is lacking.

The appropriateness of prescribing can be assessed by quality indicators. The ESAC team recently reported 3 types of disease-specific quality indicator for each of the 7 most common indications for antibiotic use in ambulatory care: 'type a', the percentage of patients receiving antibiotics with age and/or gender limitation; 'type b', the percentage of these patients prescribed the recommended antibiotics; and 'type c', the percentage of 'type a' patients prescribed quinolones. The recommended ranges were defined for each type of indicator for each indication [3].

Infections of the urinary tract (UTI) are among the most common infections in the female population. The lifetime possibility of a woman developing a UTI is 40–60% [4]. A rapid increase in resistant uropathogens is an important public health issue. With regard to UTI, acute uncomplicated cystitis covers the vast majority of encounters in general practice [5].

The aim of this study was to compare Hungarian antibiotic use in acute cystitis with the disease-specific quality indicators developed by ESAC and with the national guidelines.

Correspondence: Z. Juhasz, Division of Infectious Diseases, First Department of Internal Medicine, Faculty of Medicine, University of Szeged, Kálvária sgt. 57, H-6725 Szeged, Hungary. Tel: + 36 62 490 590/452. Fax: + 36 62 490 590/454. E-mail: dr.zoltanjuhasz@gmail.com

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Materials and methods

The crude data on systemic ambulatory antibiotic use originated from the National Health Fund Administration. The investigation period covered 6 months (January–June 2007). The analysis during this half-year used all prescriptions claimed in the community pharmacies of Hungary ($n = 2010$ pharmacies). Antibiotic use was evaluated by the Anatomical Therapeutic Chemical (ATC) classification and defined daily dose (DDD) measurement unit (version 2008). Population data were retrieved from Eurostat.

The International Classification of Diseases (ICD) codes (version 10) displayed on Hungarian prescriptions allowed the assessment of antibiotic use by indication without stratification for age and gender. The quality indicators developed by ESAC pertain to the U71 code of the International Classification of Primary Care, second revision (ICPC-2-R code). The conversion between the ICD-10 and the ICPC-2-R codes was performed by a computer programme available from the website of the Norwegian Centre for Informatics in Health and Social Care [6].

The ESAC 3a indicator represents adult female patients with cystitis (ICPC-2R: U71) receiving systemic antibacterial therapy (acceptable range 80–100%). The ESAC 3b indicator shows the percentage of 3a patients receiving the recommended antibacterials (ATC: J01EA: trimethoprim and derivatives, or J01XE: nitrofuran derivatives, or J01XX: other antibacterials; acceptable range 80–100%), whereas 3c reflects the percentage of 3a patients receiving quinolones (ATC: J01M: fluoroquinolones; acceptable range 0–5%). The ESAC 3b disease-specific quality indicator was estimated by the relative use of the ESAC recommended antibacterial agents and ESAC 3c by the relative use of quinolones in acute cystitis.

Originally ESAC recommended the use of the J01EA group (trimethoprim and derivatives) for acute cystitis, but as this ATC group is not available in Hungary we considered the use of the J01EE group (combination of sulfonamides and trimethoprim) instead of the J01EA group. The results were compared to the predefined acceptable ranges.

In 2007 there were 3 national clinical guidelines available for the treatment of acute cystitis: one was published by the Hungarian Professional College of Infectious Diseases and Urology, the second by the Hungarian Professional College of Internal Medicine and Nephrology, and the third by the Editor of the Clinical Guide to Infectious Diseases Manual. All guidelines concerned fertile female patients suffering from uncomplicated acute cystitis. Adherence to these guidelines was also calculated.

Results

For the 8 ICD codes (N3000, N3010, N3020, N3030, N3040, N3080, N3090, and N3900) that corresponded to the U71 code of the ICPC-2-R code system, the recorded antibiotic use was 1.24 DDD per 1000 inhabitant-days, representing 6.9% of all antibacterial use in the Hungarian ambulatory care sector. The 3 dominating diagnoses were acute cystitis (N3000), urocystitis (N3090), and urinary tract infection, site not specified (N3900), with a cumulative share of 94.2% within the studied indications (i.e., the 8 ICD codes belonging to the U71 code). In order to be able to compare our antibiotic use data to the national guidelines (which refer to acute cystitis cases), we focused all further calculations on the 2 dominating ICD codes that refer to acute cystitis cases: acute cystitis (N3000) and urocystitis (N3090).

Antibiotics were administered orally. The 10 antibacterials with the highest use ('top 10' agents) represented 90.4% of all systemic antibiotic use for acute cystitis. The adherence rate to different recommendations (i.e., ESAC and Hungarian guidelines) and the use of the top 10 agents are displayed in Table I.

Fluoroquinolones constituted 54.3% of the total antibiotic consumption, with 3 among the top 10 agents. The proportion of beta-lactam use was 17.0% (Table I). Co-amoxiclav was the most frequently prescribed beta-lactam (share within the penicillin group: 70.3%), followed by ampicillin and amoxicillin. Besides the most popular cephalosporin – cefuroxime (which covered 43.8% of cephalosporin use) – 3 other agents had notable use: cephalexin, cefixime, and ceftibuten. The adherence rate to the 3 available Hungarian guidelines ranged between 59.3% and 74.2%. The relative consumption of antibacterials not among the recommended agents in any Hungarian guidelines was 7.8%. The use of antibacterials recommended by ESAC (quality indicator 3b) was far below the acceptable range, while the proportion of fluoroquinolones (quality indicator 3c) exceeded the ESAC recommended range more than 10 times (Table I).

Discussion

To the best of our knowledge this is the first comprehensive, nationwide study to evaluate antibiotic use in cystitis in relation to the ESAC disease-specific quality indicators. Moreover, we evaluated the adherence to available national guidelines. Our results were well outside the acceptable ranges for the ESAC quality indicators, and national guidelines were followed in less than 75%.

Table I. Relative use of the top 10 antibacterials used in acute cystitis and their recommendation status in the different guidelines.

	Use in acute cystitis		Antibiotics recommended by the guidelines				
			National guidelines[a]			ESAC QI 3b[b]	ESAC QI 3c[c]
	DDD/1000 inhabitant-days	%	1	2	3	(AR 80–100%)	(AR 0–5%)
Total antibiotic consumption in cystitis	1.06	100%					
Top 10 antibiotics (90.41%)							
1. Norfloxacin	0.28	25.94	x	x	x		NR
2. Ciprofloxacin	0.20	18.96	x		x		NR
3. SMX–TMP	0.15	14.34		x		x	
4. Ofloxacin	0.09	8.45	x		x		NR
5. Nitrofurantoin	0.07	6.75	x	x	x	x	
6. Co-amoxiclav	0.06	5.97		x	x		
7. Cefuroxime	0.04	3.70		x	x		
8. Fosfomycin	0.02	2.22	x			x	
9. Doxycycline	0.02	2.19					
10. Nalidixic acid	0.02	1.89					
Adherence to guidelines (%)			63.3%	59.3%	74.2%	23.3%	56.2%

DDD, defined daily dose; ESAC, European Surveillance of Antimicrobial Consumption; AR, acceptable range; NR, not recommended by ESAC; SMX–TMP, sulfamethoxazole and trimethoprim; Co-amoxiclav, amoxicillin and clavulanic acid.

[a]National guidelines: 1, Guidelines of the Hungarian Professional College of Infectious Diseases and Urology; 2, Guidelines of the Hungarian Professional College of Internal Medicine and Nephrology; 3, Editorial Guidelines of the Clinical Guide to Infectious Diseases Manual.

[b]ESAC QI 3b disease-specific quality indicator: relative use of recommended antibacterials.

[c]ESAC QI 3c disease-specific quality indicator: relative use of quinolones.

Up to now, no published studies have used the disease-specific quality indicators developed by ESAC, which limits our comparison. The lack of similar studies may be due to the recent development of these indicators, but 'unknown' indication can be the major obstructive factor. The Hungarian prescription database is valuable in the sense that drug prescription is linked to diagnosis; there is a lack of linkage between drug use and diagnosis in many national prescription databases including the Scandinavian ones [7].

The adherence rate to national guidelines for cystitis varies greatly in the literature. In Finland, the recommended first-line antibiotics (trimethoprim, pivmecillinam, or nitrofurantoin) were prescribed in 66–78% of cases at healthcare centres [8]. Dutch authors found that about 75% of the antibiotic prescriptions were for first-line agents (nitrofurantoin 32.7%, sulphonamides and trimethoprim 43.3%) [9]. On the other hand, in a Spanish study, only 17.7% of patients were treated empirically with the recommended first-choice antibiotics [10]. The general lack of adherence to national guidelines has also been demonstrated among American primary care physicians. Fluoroquinolones were given in 35.4% of cases, while first-line agents sulfamethoxazole–trimethoprim (SMX–TMP) and nitrofurantoin were prescribed in 29.8% and 18.8%, respectively [11].

Our survey showed that SMX–TMP and nitrofurantoin made up 13.8% and 6.9% of antibiotics for acute cystitis, respectively. In Israel, SMX–TMP was the most frequently used agent (25% of all cases), followed by nitrofurantoin (14.7%) [12].

In Germany, fluoroquinolones were prescribed in a third of cases and an increase in Escherichia coli resistance to ciprofloxacin from 7.7% to 14.5% was detected during a 3-y-period [13].

In Hungary, the consumption of quinolones dominated in acute cystitis. According to data from the National Centre for Epidemiology, the resistance rate of E. coli to ciprofloxacin increased from 12.6% in 2005 to 22.2% in 2010 and the norfloxacin resistance rate of E. coli reached 23.4% in ambulatory patient urine cultures. As 2 out of the 3 Hungarian acute cystitis guidelines recommend the fluoroquinolone class as first-line treatment in acute non-complicated cystitis, they could be responsible for the massive fluoroquinolone use and the increase in fluoroquinolone resistance.

The low rate of nitrofurantoin use could be explained in part by its gastric and pulmonary adverse effects, which are noted in the guidelines published by the Hungarian Professional College of Urology. Secondly, permanent supply problems might impede the use of nitrofurantoin. The marginal role of fosfomycin in the treatment of acute cystitis is not surprising, as it is recommended in only one of the national guidelines.

There are some limitations to our study. The ESAC quality indicators for cystitis were defined for

female patients older than 18 y. Unfortunately we could not screen our data for sex and age, but this does not affect our results and conclusions as studies show that most acute cystitis cases occur in females of reproductive age [4].

Secondly, the Hungarian guidelines divide lower urinary tract infections into complicated and uncomplicated groups, while the ICD codes do not differentiate between these groups. As some of the agents that are recommended in the national guidelines for acute uncomplicated cystitis are not optimal for complicated cystitis (e.g., fosfomycin), the calculated adherence rates to Hungarian guidelines are slightly overestimated.

Thirdly, the ESAC quality indicators were defined for patients who should receive the recommended antibacterial agent. Unfortunately individual patient data were not available to us, only data on antibiotic consumption linked to an indication. As the prescribed DDD quantity of the different antibacterial agents used in acute cystitis did not differ considerably, the percentage of patients treated and the relative use of prescribed antibiotics is comparable.

In summary we found excessive use of fluoroquinolones for acute cystitis in Hungary. However, the pattern of use (i.e., the dominant fluoroquinolone use) was consistent with the national guidelines that were, and still are, in force. These guidelines are in contrast to the ESAC proposed acceptable range of 0–5% for quinolone use that was deemed relevant by an expert panel consisting of experts from 24 different countries in Europe and Israel.

In order to decrease fluoroquinolone use and thus stop the increasing resistance problem, the Hungarian Society of Family Physicians should compile new, primary care focused guidelines that recommend fluoroquinolones only as second-line or targeted treatment.

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Publication related to the Thesis

II.

EREDETI KÖZLEMÉNY

Az akut cystitis kezelésének hazai gyakorlata országos vényforgalmi adatok alapján

Juhász Zoltán dr.[1] ▪ Benkő Ria dr.[2] ▪ Matuz Mária dr.[2] ▪ Viola Réka dr.[2]
Soós Gyöngyvér dr.[2] ▪ Hajdú Edit dr.[1]

[1]Szegedi Tudományegyetem, Általános Orvostudományi Kar, I. Belgyógyászati Klinika, Infektológiai Osztály, Szeged
[2]Szegedi Tudományegyetem, Gyógyszerésztudományi Kar, Klinikai Gyógyszerészeti Intézet, Szeged

Bevezetés: Az akut cystitis az ambuláns ellátásban előforduló egyik leggyakoribb infekció. A kezelésére alkalmazott antibiotikumok felhasználásának elemzése és értékelése több szempontból is fontos. *Célkitűzés:* A felmérés az akut cystitisre vonatkozó hazai járó betegek antibiotikumfelhasználását értékelte. *Módszer:* Az elemzés az országos vényforgalmi adatok alapján vizsgálta az akut cystitisre vonatkozó antibiotikumfelhasználási adatokat. Az antibiotikumfelhasználás mintázatának értékelése minőségi indikátorok segítségével történt. A hazai irányelvek tartalmi összevetése mellett az irányelvekhez történő adherencia is meghatározásra került. *Eredmények:* Hazánkban az akut cystitis kezelésére ~60%-ban kinolonokat alkalmaztak, a felhasználási toplistát a norfloxacin és a ciprofloxacin vezette 26% és 19%-os részesedéssel. A nemzetközileg javasolt szerek közül a szulfonamidok részesedése 15%, a nitrofurantoiné 7%, a fosfomyciné 2% volt. A hazai irányelvekhez való adherencia átlagosan 66% volt, a felmérés az irányelvek problematikus pontjait azonosította. *Következtetések:* Az antibiotikumrendelés gyakorlata akut cystitisben a nemzetközi minőségi indikátorok tükrében nem optimális. Az aktuális hazai rezisztenciaviszonyok ismeretében egy új, egységes kezelési irányelv kidolgozása indokolt. Orv. Hetil., 2014, *155*(15), 590–596.

Kulcsszavak: cystitis, antibiotikumfelhasználás, minőségi indikátorok, adherencia, hazai irányelvek

Treatment practice of acute cystitis on the basis of national prescription data

Introduction: Urinary tract infections are one of the common diseases in the primary health care. *Aim:* To analyse patterns of ambulatory antibiotic use in acute cystitis. *Method:* Antibiotic use data was based on national-level prescription turnovers. Patterns of antibiotic use were evaluated by prescribing quality indicators. The content of different national guidelines for treatment of acute cystitis and adherence to these guidelines were also evaluated. *Results:* For the treatment of acute cystitis quinolones were used predominantly. Norfloxacin (26%) and ciprofloxacin (19%) were prescribed most commonly. The use of internationally recommended agents such as sulphonamides, nitrofurans and fosfomycin shared 15%, 7% and 2%, respectively. The average adherence rate to national guidelines was 66% and certain weak points (e.g. controversial content) of the national guidelines were also identified. *Conclusions:* Antibiotic use in acute cystitis seems to be suboptimal in Hungary. Considering actual local antibiotic resistance patterns, a new national guideline should be worked out for acute cystitis treatment.

Keywords: cystitis, antibiotic use, quality indicators, adherence, national guidelines

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Rövidítések

AMC = amoxicillin és klavulánsav; ATC = Anatomical Therapeutic Classification; BNO = Betegségek Nemzetközi Osztályozása; DDD = Defined Daily Dose; EARSS = European Antimicrobial Resistance Surveillance System; ECDC = European Centre for Disease Prevention and Control; EMMI = Emberi Erőforrások Minisztériuma; ESAC = European Surveillance of Antimicrobial Consumption; ESBL = extended spectrum beta-lactamase; ESzCsM = Egészségügyi, Szociális és Családügyi Minisztérium; GYEMSZI = Gyógyszerészeti és Egészségügyi Minőség- és Szervezetfejlesztési Intézet; ICPC-2R = International Classification of Primary Care – second Revision; OEK = Országos Epidemiológiai Központ; OEP = Országos Egészségbiztosítási Pénztár; SMX-TMP = sulfamethoxazol és trimethoprim; WHO = World Health Organization

Ismert tény, hogy az antibiotikumok nem kellő körültekintéssel történő, túlzott használata növeli a velük szembeni rezisztenciát [1]. Az antibiotikumfogyással kapcsolatos mennyiségi adatok évekre visszamenően rendelkezésre állnak, mivel hazánk csatlakozott az antibiotikumfogyást monitorizáló európai hálózathoz (European Surveillance of Antimicrobial Consumption, ESAC-Net), amely immár az Európai Betegségmegelőzési és Járványügyi Központ (European Centre for Disease Prevention and Control, ECDC) szervezetének része. Magyarország, a 2010. évi adatok szerint, az ambuláns antibiotikumfelhasználás mennyiségét tekintve a középmezőny végén állt az Európai Unió országai között [2]. A felhasznált mennyiségen túl azonban fontos az antibiotikumfogyás mintázata, az antibiotikumrendelések indikációja, illetve az egyes indikációkban a meghatározott/elvárt terápiás gyakorlathoz való viszonya. Az ambuláns antibiotikumfelhasználás minőségére vonatkozóan a korábbiakban *Katona Zoltántól* jelentek meg közlemények, cikkeinek fókuszában a légúti betegségek kezelése állt [3, 4].

Az alapellátásban az antibiotikumrendelés második leggyakoribb indikációja a húgyúti fertőzés. Gyakrabban fordul elő nőknél, prevalenciája 40–60% közötti a szexuálisan aktív fiatal nők körében [5, 6, 7]. Globálisan fontos közegészségügyi és klinikai kihívást jelent az uropatogén kórokozók növekvő rezisztenciája [8].

A bizonyítékokon alapuló orvoslástól, az ajánlott kezelésektől való eltérés mérésére a minőségi indikátorok alkalmazása lehetőséget biztosít. Az ESAC szakmai csoportja három évig tartó munkamenet során (2008–2011) betegségspecifikus minőségi indikátorokat fejlesztett ki és publikált. Három indikátortípust határoztak meg a járóbeteg-ellátásban előforduló hét leggyakoribb fertőzéses megbetegedésre, köztük a cystitisre. A minőségi indikátorok *a)* az antibiotikumokkal kezelendő betegek arányára, *b)* az adott kórképre vonatkozóan az ajánlott antibiotikumok optimális felhasználási arányára és *c)* a kinolonok maximálisan elfogadható felhasználásbeli részesedésére vonatkoztak [9].

Felmérésünk bemutatja és értékeli a hazai ambuláns antibiotikumfogyást akut cystitisben. A kórkép kezelésére alkalmazott antibiotikumok felhasználását az ESAC által publikált minőségi indikátorokkal, valamint a 2007-ben érvényben lévő hazai szakmai irányelvekkel vetettük össze.

Módszer

Az antibiotikumfelhasználásra vonatkozó adatok az Országos Egészségbiztosítási Pénztár (OEP) adatbázisából származtak, amely az összes hazai közforgalmú gyógyszertár (2007-ben: 2010 gyógyszertár) teljes vényforgalmát tartalmazza. A vizsgálat időtartama hat egymást követő hónapra (2007. január–június) terjedt ki. Az antibiotikumfelhasználás statisztikai mérésére az Egészségügyi Világszervezet (WHO) által használt anatómiai, terápiás, kémiai osztályozási rendszert (Anatomical Therapeutic Classification, ATC) és a meghatározott napi adagot (Defined Daily Dose, DDD; 2010-es verzió) használtuk.

A társadalombiztosítási támogatással rendelhető gyógyszerekről és a támogatás összegéről szóló, jelenleg is hatályban lévő jogszabály – 1/2003. (I. 21.) ESzCsM rendelet – alapján a vényeken kötelező feltüntetni az adott gyógyszer rendelésének alapjául szolgáló Betegségek Nemzetközi Osztályozása (BNO) szerinti kódokat. A BNO-kódokat a gyógyszerkiadás során rögzítik a gyógyszertári elszámolórendszerben, amely lehetővé teszi az OEP adatbázisából a diagnózis szerinti adatlekérdezést.

A minőségi indikátorokról publikált ESAC-cikkben egy alapellátásban alkalmazott kódrendszert használtak (International Classification of Primary Care, ICPC-2R), ezért ezt egy számítógépes programmal BNO-kódokká konvertáltuk [10].

Az ESAC által kifejlesztett, cystitisre vonatkozó minőségi indikátorok a következők:

- *ESAC 3a indikátor*: Azon 18 év feletti női betegek aránya, akik cystitis tüneteivel fordultak orvoshoz és antibiotikumot írtak fel számukra. Az ESAC által megadott optimális tartomány: 80–100%.
- *ESAC 3b indikátor:* Az előző csoport tagjai közül azon betegek százalékos aránya, akik a következő (ESAC által javasolt) antibiotikumok valamelyikét kapták:
  - J01EA: trimethoprim és származékai (Magyarországon a trimethoprim és szulfonamidok kombinációja érhető el: J01EE),
  - J01XE: nitrofuránszármazékok,
  - J01XX: egyéb antibiotikumok (hazánkban elérhető: fosfomycin).

A kívánatos tartományt ebben az esetben 80–100% között határozták meg.

- *ESAC 3c indikátor:* Azon betegek százalékos aránya a 3a indikátorcsoportból, akik kinolonkezelésben része-

sültek (ATC: J01M-kinolonok). Az optimális tartomány: 0–5%.

Magyarországon 2007-ben három különböző szakmai irányelv volt érvényben akut cystitis kezelésére:

1. Urológiai Szakmai Kollégium és Infektológiai Szakmai Kollégium által kiadott [11],
2. Belgyógyászati és Nefrológiai Szakmai Kollégium által közölt [12],
3. az Infektológiai Útmutató Szerkesztőségi Irányelve a húgyúti fertőzések kezeléséről [13].

A nemzetközi minőségi indikátorokkal való összevetés mellett elemzésünk kiterjedt ezen irányelvekhez történő adherencia vizsgálatára, valamint az irányelvek tartalmi és formai összehasonlítására.

Eredmények

Az OEP adatbázisa szerint 2007 első hat hónapjában a hazai járóbeteg-ellátásban az antibiotikumok 6,9%-át – mintegy 1,1 DDD/1000 fő/nap mennyiséget – írták fel cystitis diagnózisra a következő BNO-kódokkal: N3000 (cystitis acuta), N3010 (interstitialis cystitis), N3020 (egyéb idült cystitis), N3030 (trigonitis), N3040 (irradiációs cystitis), N3080 (egyéb cystitis), N3090 (urocystitis).

A cystitis acuta (N3000) és az urocystitis (N3090) diagnózisok lefedték a cystitisre történő antibiotikumfelhasználás 93,7%-át. Mivel mind a három hazai szakmai irányelv akut cystitis kezelésére vonatkozott, ezért a továbbiakban ezen két domináns diagnózishoz kapcsolódó antibiotikumfogyási adatokat elemeztük. A leggyakrabban rendelt szerek, illetve a különböző irányelvek által ajánlott hatóanyagok az *1. táblázatban* láthatóak.

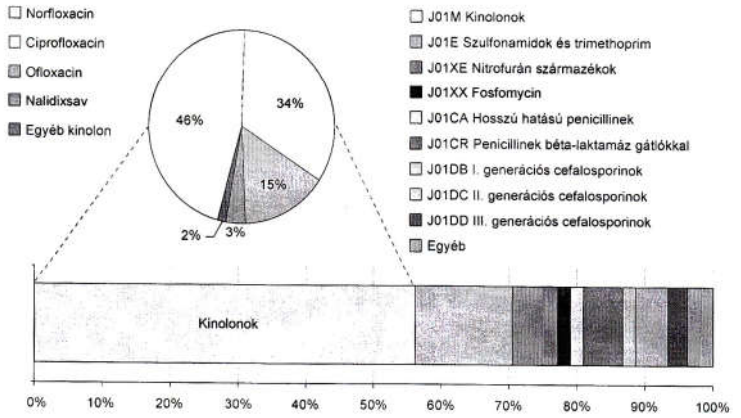
A cystitisben tíz leggyakrabban rendelt antibakteriális hatóanyag az összes (tudnillik akut cystitisre alkalmazott) antibiotikumfogyás 90,4%-át adta *(1. táblázat)*. Kiemelendő, hogy a kinolonok fogyása erősen dominált, a cystitisre felírt antibiotikumok közel 60%-át adta. A második leggyakrabban alkalmazott antibiotikumcsoport a béta-laktámok, 17%-kal részesedtek az antibiotikumfogyásból.

Az akut cystitisben alkalmazott antibiotikumcsoportok és a kinolonok csoportjának hatóanyag szerinti megoszlását az *1. ábrán* tüntettük fel.

Az antibiotikumfelhasználás mintázata alapján a három különböző szakmai irányelv közül legnagyobb mértékben az Infektológiai Útmutató Szerkesztőségi Irányelvét (74,2%), majd az Urológiai és Infektológiai Szakmai Kollégium által készítettet (63,3%), végül legkisebb mértékben a Belgyógyászati és Nefrológiai Szakmai Kollégiumét (59,3%) követték az orvosok a gyógyszerrendelés során.

Az ESAC által cystitis kezelésére javasolt antibiotikumok részesedése felmérésünkben 23,3% volt, az idetartozó 3b minőségi indikátor optimális tartományával (80–100%-kal) szemben. Lebontva hatóanyagszintre a nemzetközileg ajánlott szereket, a trimethoprim-sulfamethoxazol részesedése 15%, a nitrofurantoiné 7%, a fosfomyciné 2% volt. A kinolonok 58,1%-os részesedése jóval meghaladta a 3c minőségi indikátor által maximálisan elfogadható 5%-ot, használatukat mindhárom hazai irányelv javasolta *(1. táblázat)*.

Az egyes irányelvek közötti tartalmi különbségeket részletesen a *2. táblázatban* foglaltuk össze. A komplikált és nem komplikált húgyúti infekciókat mindhárom irányelv elkülönítette. A szövegben referenciákat, valamint magyarázattal kiegészített evidencia- és ajánlásszinteket egyedül az urológiai-infektológiai irányelv közölt. Kiegészítő kezelést az Urológiai, megelőző intézkedést (például tőzegáfonya) pedig a Belgyógyászati és Nefrológiai Szakmai Kollégium irányelve javasolt.



1. ábra | Akut cystitisben alkalmazott antibiotikumcsoportok és a kinolonok csoportjának hatóanyag szerinti megoszlása (Egyéb kinolonok: levofloxacin, pefloxacin, moxifloxacin)

Az első és másodvonalbeli szereket kizárólag a belgyógyászati irányelv különítette el. A kinolonrezisztencia emelkedő tendenciáját az urológiai-infektológiai és a belgyógyászati irányelv említette, az előbbi azonban kiemelte, hogy a rövid távú kinolonkezelés rezisztencia-indukáló hatása nem volt bizonyított. Az egyes gyógyszerek (például kinolonok) főbb mellékhatásaira az irányelvek egyáltalán nem tértek ki, kivéve a nitrofurantoin mellékhatásaira az urológiai-infektológiai irányelv szöveges részében.

Az urológiai-infektológiai irányelvben mind a trimethoprim-sulfamethoxazol, mind a béta-laktámok, mind a nitrofurantoin empirikus terápiában való alkalmazhatóságát illetően nehéz levonni egyértelmű állásfoglalást, mivel ellentmondás van a szöveges rész és a táblázat között, továbbá a táblázat Megjegyzés rovata néhány esetben nehezen értelmezhető. (Az *1. táblázatban* az adott hatóanyag ajánlott voltát az egyes irányelvek táblázatai alapján határoztuk meg.)

Megbeszélés

A nem komplikált húgyúti fertőzés az egyik leggyakoribb, alapellátásban előforduló betegségtípus, amely miatt csak az Egyesült Államokban évente 7 millió ember keresi fel orvosát [14, 15].

A jelen felmérés átfogó képet ad az egyik leggyakoribb ambuláns fertőző betegségre, az akut cystitisre vonatkozó antibiotikumfogyásról, és értékeli az antibiotikumfelhasználás összetételét.

Eredményeink alapján elmondhatjuk, hogy a hazai irányelvek követése átlagban közel 70% volt, a nemzetközi minőségi indikátorok tekintetében pedig a hazai antibiotikumfelhasználást tükröző indikátorértékek messze elmaradtak a kívánatostól.

A jelenség nem egyedülálló hazánkban, *Katona Zoltán* korábban az alapellátásban előforduló légúti fertőzések elemzése kapcsán írt le szuboptimális antibiotikumalkalmazást [3, 4].

A cystitisre vonatkozó szakmai ajánlásokhoz történő adherencia a külföldi szakirodalomban változatos képet mutat. Hollandiában az antibiotikumrendelések 75%-ában első vonalbeli szereket írtak (nitrofurantoint és trimethoprim-sulfamethoxazolt) [16]. Hasonlóan magas arányt közölt *Rautakorpi* Finnországból, ahol az alapellátásban rendelt antibiotikumok 66–78%-a az elsőként javasolt szerek közül volt [17]. Spanyol felmérések a fentiektől eltérő adatokat mutattak: az elsőként ajánlott antibiotikumok mindössze 17%-ban kerültek felírásra [18]. Az Amerikai Egyesült Államokban az alapellátásban az első vonalbeli trimethoprim-sulfamethoxazolt 30%-ban választották az orvosok [19].

A minőségi indikátorokat tekintve – külföldi közlések híján – adatainkat direkt módon nehézkes más felmérésekkel összehasonlítani. Ennek oka egyrészt az ESAC minőségi indikátoroknak a közelmúltban történő publikálása [9], valamint a külföldi gyógyszeradatbázisok álta-

1. táblázat | Akut cystitisben leggyakrabban használt tíz antibiotikum felhasználása és ajánlása az egyes irányelvekben

Hatóanyag	Antibiotikumhasználat akut cystitis kezelésében		Hazai irányelvek ajánlása		
	DDD/1000 lakos/1nap	%	1	2	3
1. Norfloxacin	0,28	25,94	Igen	Igen	Igen
2. Ciprofloxacin	0,2	18,96	Igen		Igen
3. SMX-TMP	0,15	14,34	Igen*	Igen	
4. Ofloxacin	0,09	8,45	Igen		Igen
5. Nitrofurantoin	0,07	6,75	Igen**	Igen	Igen
6. AMC	0,06	5,97		Igen	Igen
7. Cefuroxim	0,04	3,7		Igen	Igen
8. Fosfomycin	0,02	2,22	Igen		
9. Doxycyclin	0,02	2,19			
10. Nalidixsav	0,02	1,89			

Irányelvek:
1: Az Urológiai és Infektológiai Szakmai Kollégium irányelvének táblázata alapján.
2: A Belgyógyászati Szakmai Kollégium és a Nephrologiai Társaság irányelvének táblázata alapján.
3: Az Infektológiai Útmutató Szerkesztőségi Irányelvének táblázata alapján.

Igen: Ajánlott szer az adott irányelv szerint.
* A táblázat megjegyzésében említi, hogy ha az antibiotikumrezisztencia elér egy bizonyos százalékot, akkor nem lehet használni, de az nem derül ki, hogy hazánkban mennyi ez az érték.
** A táblázat megjegyzésében a nitrofurantoin „alacsony" (77–83%) eradikációs képességét említi.

SMX-TMP = sulfamethoxazol és trimethoprim; AMC = amoxicillin és klavulánsav

2. táblázat | A vizsgálat ideje alatt érvényes, az akut cystitis kezelésére vonatkozó hazai irányelvek tartalmi és formai összehasonlítása

	Hazai irányelvek		
	1	2	3
Komplikált, nem komplikált kórformák elválasztása	+	+	+
Betegpopuláció megjelölése nemek szerint	+	+	+
Betegpopuláció megjelölése életkor szerint	+	+	–
Megelőző intézkedés ajánlása (például tőzegáfonya)	0	+	0
Kiegészítő kezelés ajánlása (például fájdalomcsillapító)	+	0	0
Kémiai rutin-vizeletvizsgálatot javasol-e?	+	+	0
Szöveg közti hivatkozások	+	0	0
Terápia időtartamának megadása	+	+	+
Ajánlás és evidenciaszintek közlése magyarázattal	+	0	0
Első és másodvonalbeli terápia megkülönböztetése	0	+	0
Folyamat ábra/táblázat segíti-e a terápiás döntést?	+	+	+
Összhang az ábra/táblázat és a szöveg között	0	+	NÉ
Antibiotikumrezisztencia hangsúlyozása	+	+	0

Rövidítések:
1: Az Urológiai és Infektológiai Szakmai Kollégium irányelve
2: A Belgyógyászati Szakmai Kollégium és a Nephrologiai Társaság irányelve
3: Az Infektológiai Útmutató Szerkesztőségi Irányelve

+: igen; 0: nem; NÉ: nem értelmezhető

lános limitációja: a gyógyszerfelírásokat nem tudják közvetlen indikációhoz kötni [20]. A hazai orvosi vényírási gyakorlat óriási előnye, hogy lehetőséget ad a gyógyszerrendelés indikáció szerinti elemzésére.

A hazai 60% körüli kinolonalkalmazással szemben Törökországban [21] 26%-ban alkalmaztak kinolonokat az akut cystitis kezelésére. Ugyanezen hatóanyagcsoportot az Egyesült Államokban 35%-ban rendelték nem komplikált húgyúti fertőzések kezelésére [19]. Ezen értékek mind jóval felette vannak az ESAC által ajánlott értéknek (0–5%). A túlzott kinolonfelhasználás egyik káros következményeként a hazai *E. coli* ciprofloxacinrezisztencia a 2006-os 14,6%-ról 2011-re 21,3%-ra növekedett nem invazív mintákból [invazív mintáknál már 2005-ben átlépte a 20%-os értéket az *E. coli* fluorokinolonrezisztenciája az Európai Antibiotikum Rezisztencia Surveillance Hálózat (EARSS-Net) adatai alapján] [22, 23]. A gyakori kinolonalkalmazás magyarázata lehet, hogy a 2007-ben elérhető hazai irányelvek közül valamennyi javasolta a kinolonokat az akut cystitis empirikus kezelésére *(1. táblázat)*.

Egy törökországi kis esetszámú felmérés szerint a nem komplikált húgyúti fertőzésben szenvedő betegeknél a leggyakrabban rendelt hatóanyagok közel fele trimethoprim-sulfamethoxazol volt [21]. Izraeli szerzők akut cystitis kezelésében rendelt szerek negyedében trimethoprim-sulfamethoxazolt találták, amely mellett másodikként a nitrofurantoin (15%) szerepelt [24].

Nálunk a trimethoprim-sulfamethoxazol az antibiotikumfogyást tekintve a harmadik leggyakrabban rendelt szer volt akut cystitisben, 10% feletti relatív részesedéssel.

A belgyógyászati szakmai irányelv [12] javasolta a sulfamethoxazol-trimethoprim alkalmazását 3 napos kezelésre, a szerkesztőségi irányelv [13] egyértelműen nem ajánlotta, míg az urológiai-infektológiai [11] irányelvben nem egyértelmű az állásfoglalás. (A szöveges rész egy viszonylag csekély esetszámú tanulmányt említ irodalmi hivatkozás – így azonosíthatóság – nélkül, amelyben az *E. coli* sulfamethoxazol-trimethoprim rezisztenciája a 21%-ot meghaladta, ezért empirikusan nem ajánlotta használatát.) Megfelelő minőségű és mennyiségű rezisztenciaadat hiánya miatt a trimethoprim-sulfamethoxazol empirikus használatának létjogosultságát nem lehet (és nem lehetett) retrospektíve (a 2007-es évre vonatkozóan) értékelni. A nemzetközi minőségi indikátortól való eltérés foka az ajánlott szerek felhasználása tekintetében (23,3% vs. ideálisan 80–100% avagy 37,6% vs. 80–100%) azonban akkor is magas, ha feltételezzük, hogy a trimethoprim-sulfamethoxazol alkalmazásának hazánkban korábban sem volt létjogosultsága.

Az országos adatbázisban sulfamethoxazol-trimethoprimról 2008-tól találhatunk vizeletből izolált *E. coli* törzsekre vonatkozó adatokat, és 2010-től választották külön a járó és a fekvő betegek vizeletmintáiból izolált törzsekre vonatkozó antibiotikumrezisztencia-adatokat [22]. Ezek alapján a rezisztencia fokozatosan emelkedik, ezért a sulfamethoxazol-trimethoprim empirikus alkalmazása nem lenne javasolható a továbbiakban cystitisben.

A nitrofurantoint világszerte már több mint 50 éve használják húgyúti fertőzések terápiájában, a fosfomy-

cint pedig közel 30 éve alkalmazzák. Hazánkban marginálisan, mindösszesen 9%-ban alkalmazták ezen hatóanyagokat.

A fosfomycin alacsony részesedési arányát magyarázhatja, hogy csupán az urológiai és infektológiai irányelv javasolta, míg a nitrofurantoint ugyan a belgyógyászati, urológiai és szerkesztőségi irányelv is ajánlja, de nem kellően hangsúlyozták szöveges részben a terápiában betöltött szerepüket, hatásukat.

Az urológiai-infektológiai irányelv [11] kifejezetten „elbizonytalanít" a nitrofurantoin alkalmazással kapcsolatban a szer alacsony eradikációs képességét, valamint akut és krónikus tüdőszindrómát okozó mellékhatását említve.

A fosfomycin antimikrobás spektruma és tolerálhatósága ideális antibiotikummá teszi a nem komplikált cystitis empirikus kezelésében, valamint a széles spektrumú béta-laktamázokat (ESBL) termelő törzsek ellen is hatékony [25, 26].

A nitrofurantoin alacsony dózisban bakteriosztatikus, magas dózisban baktericid, per os alkalmazva a vesén keresztül kellően magas koncentrációban választódik ki a vizeletbe, ESBL-termelő *E. coli* ellen is hatékonynak találták [27].

Emellett mindkét hatóanyag érzékenységi értékei kedvezőek. Az Országos Epidemiológiai Központ (OEK) adatai alapján nitrofurantoinra az *E. coli* törzsek 96,1%-a volt érzékeny 2012-ben [22]. A fosfomycinre vonatkozóan nemzetközi adatok állnak csak rendelkezésre, amelyek szerint a multirezisztens, ESBL-termelő Enterobacteriaceae törzsek érzékenysége is 90% feletti volt [25].

A járóbeteg-ellátásban használatos béta-laktámok, szintén használhatók akut cystitis kezelésében. Hatékonyságukat rövid és hosszú távú kezelésben a sulfamethoxazol-trimethoprimmal egyenértékűnek találták [28, 29]. A három hazai irányelv nem volt egységes a megítélésükben: a szerkesztőségi irányelv 5 napos kezelésre javasolt orális II–III. generációs cefalosporinokat, az első generációs cefalosporinokat azonban a magas rezisztenciaviszonyokkal magyarázva nem ajánlotta empirikusan [13]. A belgyógyászati irányelv a klavulánsavval/sulbactammal kombinált aminopenicillinkészítményeket, illetve az első generációs cefalosporinokat az akut cystitis első vonalbeli empirikus kezelésére ajánlotta [12]. Az urológiai és infektológiai irányelv a táblázatában nem ajánlott egyetlen béta-laktám antibiotikumot sem, szövegesen 5 napos kezelésben javasolta a béta-laktámokat, hatóanyag- és csoportspecifikáció nélkül [11].

Egyes cefalosporinok akut cystitisben való alkalmazhatóságát alternatív szerként az európai húgyúti kezelésről szóló irányelv javasolja [30, 31], a kedvező hazai rezisztenciaviszonyok pedig ezt lehetővé is teszik (járó betegek vizeletmintáiból izolált E. coli cefuroximrezisztenciája 2012-ben 6,8%, a cefiximé 6,6% volt) [22].

Az irányelvek formai és tartalmi jellemzőinek ismertetése során azonosítottunk néhány szerkesztési hiányosságot (például szövegközti referenciák hiánya), illetve ellentmondást (például urológiai-infektológiai irányelvben táblázat vs. szöveges rész), amelyek megnehezíthetik a szakmai ajánlások értelmezését és a kezelőorvos terápiás döntését. Ezen hiányosságok felfedése segítheti a jövőbeni irányelv-fejlesztői munkát.

Felmérésünket az alább felsorolt tényezők limitálták, azonban ezek egyike sem befolyásolja érdemben az eredményeinket és a levont következtetéseket.

Elsőként említhető, hogy a BNO-kódok nem tették lehetővé a komplikált–nem komplikált kórformák közötti különbségtételt, mivel csak egységesen vonatkoznak a cystitis diagnózisra. Továbbá életkorra és nemre sem tudtuk adatainkat szűrni, de korábbi irodalmi adatok alapján feltételezzük, hogy a jelen tanulmányban elemzett fertőzések túlnyomó része nem terhes nőkben előforduló nem komplikált cystitis volt [32, 33].

Az ESAC által definiált minőségi indikátorok az antibiotikumkezelésben részesült egyének százalékos arányára vonatkoznak. Betegszintű adatok nem álltak rendelkezésünkre, ezért az indikációhoz kötött relatív antibiotikumfogyás oldaláról végeztük el az elemzést.

Javaslatunk szerint a jelenlegi hazai rezisztenciaviszonyok függvényében első vonalbeli kezelésként a nitrofurantoin és fosfomycin, valamint alternatív szerekként II–III. generációs orális cefalosporinok (például cefuroxime, cefixim) lennének ideálisak.

Következtetések

Az antibiotikumpolitika kulcsfontosságú napjaink egészségügyi rendszerében, amelynek egyik pillére a racionális antibiotikumrendelési gyakorlat. Közleményünk rávilágít az antibiotikumfelhasználás minőségi problémáira, a fluorokinolonok túlzott használatára a húgyúti fertőzésekben.

A húgyúti fertőzések kezelését meghatározó különböző tartalmú ajánlások közötti ellentmondás feloldására egy egységes, könnyen áttekinthető irányelvre van szükség, amely figyelembe veszi a hazai rezisztenciaviszonyokat és hozzáférhető minden alapellátásban dolgozó orvos számára.

Ezt a törekvést segíti a jelenlegi egészségpolitika, mivel a szakmai irányelvek revíziója, megújítása jelenleg nagy erővel folyik az Egészségügyi Szakmai Kollégium Tagozatai és Tanácsai által, a Gyógyszerészeti és Egészségügyi Minőség- és Szervezetfejlesztési Intézet (GYEMSZI) koordinálásával [18/2013. (III. 5.) EMMI rendelet]. Cél az irányelvek egységesítése, a fejlesztésük során az esetleges külső befolyástól mentesség követelménye.

Az új irányelvek bevezetését követően további és folyamatos felmérések szükségesek a terápiás ajánlások (köztük a húgyúti fertőzésé) megfelelő betartásának monitorozására.

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(Juhász Zoltán dr.,
Szeged, Kálvária sugárút 57., 6725
e-mail: dr.zoltanjuhasz@gmail.com)

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