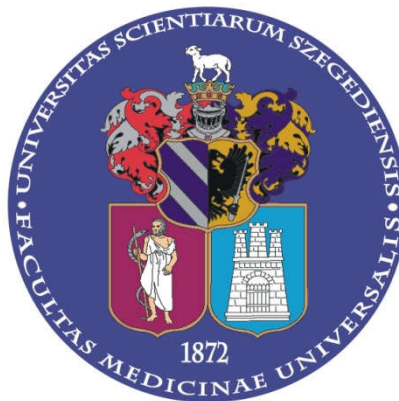# Evaluation of the Hungarian ambulatory antibacterial use in urinary tract infections with different methods

Summary of Ph.D. Thesis

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1. INTRODUCTION

One of the most important public health achievement of the XX. century was the discovery of antimicrobial agents. Since then mortality rates of infectious diseases decreased considerably in high-income countries. After the discovery of penicillin in 1929, until 1950 more than 100 antibiotics were known. 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. 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. Drug resistant strains appeared first in hospitals where most antibiotic were administered initially. 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.

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. The use of quionolones 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.

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

There are increasing international concerns that many prescribing may be unnecessary or irrational (overuse of certain type of drugs) and not without dangers. Common problems identified in hospital and ambulatory care could contribute to antibiotic resistance and poor outcomes of patients, decreasing the quality of healthcare.

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

Practice guidelines are important means of healthcare quality improvement in many European countries. 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 and great oppurunity for national and international comparisons. It is usually not enough to measure the consumption of the medications, we also have to measure its quality.

Quality indicators are focusing on different aspects of quality: effectiveness, safety, appropriateness, costs, compliance, pesistance and should be relevant for clinical practice.

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

The European Surveillance of Antimicrobial Consumption (ESAC) project started in November 2001. The project was funded by grants of the European Commisssion and the University of Antwerp, Belgium.

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.

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 imitation prescribed an antibiotic for sístemic use, and receiving the guideline recommended antibiotic

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

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.

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.

There are some international articles and only a few Hungarian works dealing with the quality of antibiotic consumption in the ambulatory care, even with prescribing quality indicators.

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.

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

- Systemic antibiotics play a key role in the outpatients care.

- 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 which enables in-depth analysis of ambulatory antibiotic use in cystitis has never been published in Hungary.

Urinary tract infections (UTI) belong to the most common diseases in the primary care. 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. More than 80% of the patients were female. Economical data relating to the health costs of UTI in Hungary have not yet been published.

Specific populations with increased risk for UTI include infants, elderly, pregnant women, patients with diabetes, underlying urological abnormalities (eg. kidney stones). 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). 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). Acute uncomplicated cystitis, a superficial infection in the bladder mucosa, accounts for the 95% of urinary tract disorders.

The vast majority of urinary tract infections is monobacterial and caused by *E.coli* in 75-95% of uncomplicated cases. *Klebsiella pneumoniae* are isolated in 10-12%, *Proteus mirabilis* in 7-9%, *Staphylococcus saprohyticus* in 5-15% of cases. Parallel with the overuse of certain groups of antibiotics, the resistance rate of uropathogens is increasing. ESBL-producing *E. coli* and *K. pneumoniae* and other resistant Gram negatives are being isolated more frequently from outpatient samples.

2. AIMS

2.1. 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

2.2. Regional ambulatory patient-level antibiotic use survey

- To study patient characteritics (age, gender, symptoms, chronic 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

3. METHODS

3.1. 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.

3.2. 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 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.

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

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 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 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 (published by the **Hungarian Professional College of Infectious Diseases and Urology,** by the **Hungarian Professional College of Internal Medicine and Nephrology** and by by the **Editor of the Clinical Guide to Infectious Diseases Manual**)

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.

3.3. 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 (GPs), 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. 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.

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 occured in otherwise healthy women and complicated if it occured 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, immunosupression. 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).

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 definied 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 to conduct patient follow up (i.e. re-consultation, therapy failure, 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.

4. RESULTS

4.1. 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 resistance rates of ciprofloxacin increased substantially, from 11.6% in 2006 to 22.2 by 2010 in outpatient samples, although there was a slight decrease in the last two years.

The proportion of beta-lactam use was 17.0%. 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.

During the comparison of the three gudelines some deficiencies and contradictions were also identified.

4.2. 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).

		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 1. Patients' main characteristics

The majority of patients were females with acute uncomplicated cystitis. Complicating factors were present in every fourth patient. 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. 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. Only the therapeutic

pattern of acute recurrent cystitis 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 was prescribed only in one third of acute uncomplicated cystitis cases.

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

5. DISCUSSION

5.1. 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. 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%). In **Finland**, the recommended first-line antibiotics (trimethoprim, pivmecillinam, or nitrofurantoin) were prescribed in 66 – 78% of cases at healthcare centres. In our study we focused the analysis only on primary care, however, the type of the health care settings may influence the adhence 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%).

On the other hand, in a **Spanish** study, only 17.7% of patients were treated empirically with the recommended first-choice antibiotics. 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.

In a recent **American** article investigating the concordance with the IDSA guidelines for uncomplicated ÚTI found that overall concordance was 33.96%, 64% of patient were prescribed an antibiotic concordant with the current IDSA guidelines.

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, 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%. 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.

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 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.

Particularly heavy fluoroquinolone prescription rates were reported from Italy (65% of prescriptions), Spain (73%), Portugal (61%), France (57%), Switzerland (64%) and Belgium (63%). (174) The fluoroquinolones were the most commonly prescribed agents in uncomplicated urinary tract infections in latvian general practices.

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).

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%. The consumption rate of internationally preferred agents, nitrofurantoin and fosfomycin were considerably low in Hungary.

Nitrofurantoin and fosfomycin-trometamol have excellent in vitro antimicrobial effects, and presereved their activity against the most common uropathogens despite the increasing antibiotic resistance. 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. Administration of nitrofurantoin may contribute to a reduction in overall quinolone use and thus help to reduce selection pressure for increased fluroquinolone resistance.

Nitrofurantoin was prescribed as often as quionolones in Canada, whereas the prescription rate of fosfomycin was only 1.9% in Canada. Fosfomycin trometamol has been extensively used in several European countries for single dose therapy in uncomplicated urinary tract infections After many years of use, fosfomycin-trometamol continues to be active against the most common uropathogens. Its 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 UTI.

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%. 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.

Beta-lactams should also be considered in the therapy of uncomplicated cystitis in primary care, but there are country specific differences. 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, the German National Guideline.

Cephalosporins are often not effective against ESBL-producing bacteria. Since 2014 the European Association of Urology does not suggest cefpodoxime-proxetil as an alternative agent. Amoxicillin-clavulanic acid could be an option for oral treatment of ESBL-associated uncomplicated UTI. 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%. In Singapore amoxicillin-clavulanic acid was the first choice in empirical treatment in UTI because of high resistance rates of uropathogens to quinolones and cotrimoxazol.

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, the *internal medicine guideline* suggested clavulanic acid/sulbactam aminopenicillines and first generation cephalosporins in the emiprical treatment of acute cystitis and 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.

Pivmecillinam, a beta-lactam and a prodrug of mecillinam, has been used for the treatment of acute uncoplicated 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 othet *Enterobacteriaceae* (including ESBL-producers). 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). It may spare the use of other agents such as TMP/SMX and fluoroquinolones where there are concerns about *E.coli* resistance in the community. 20-30% of prescriptions for acute cystitis in Denmark, Sweden, Norway are for pivmecillinam.

5.2. 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.

In comparable studies 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, 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. Urine dipstick was requested in majority of cases similar to the Spanish UTI study. 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. In complicated cystitis and in pyelonephritis investigation of urine culture is mandatory in all cases. Symptomatic relief offered by *pain killers* are increasingly recognized as important in treatment of UTI however advocated by only a few guidelines. Analgesics were given to minority of patients in this study which is not suprising as neither the European guideline, nor the valid national guideline (2010) discuss this therapeutic opportunity in UTI.

Usage of fluoroquinolones dominated in all UTI types. Common ambulatory use of fluoroquinolones in treatment of UTIs has been reported from other European studies as well. However low rate of fluoroquinolone use (6%) in this disease has been reported from Norway. Fluoroquinolones are considered as critically important antibiotics according to the WHO classification 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. In several countries including Hungary fluoroquinolone resistance of *E. coli* exceeds 20% in non-invasive ambulatory samples, therefore their use in empirical treatment of UTI should be re-evaluated.

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*, therefore the recorded fosfomycin use should be regarded inappropriate in these cases. The low perscription rate for **nitrofurantoin** in uncomplicated cystitis was not suprising as national guideline emphasize its low eradication rate. As a consequence many pharmacies would not stock them, resulting limited availability.

For uncomplicated cystitis the European guideline only recommends **pivmecillinam**, which is not yet available in Hungary. Hungarian national guidelines recommend **co-amoxicillin-clavulanic acid** as first line treatment which explaines 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. 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.

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 which can - at least partly – be explained by the lack of suitable packages for short term antibiotic courses. In Hungary –with the exception of fosfomycin - the available antibacterial packages used in UTIs (fluoroquinolones, beta-lactams) are not designed for short-term therapy and current reimbursement policy does not allow splitting marketed packs of medications. Moreover, indicating therapy duration is not a compulsory element of any drug perscriptions, all which suggests to GPs that antibiotic course duration should be set to the individual case.

6. CONCLUSION

In my PhD thesis I set out to demonstrate the outpatient antibiotic use pattern in cystitis in Hungary. 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 cytitis 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. The overuse of quinolones 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 emprical 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 recommendatons 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.

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 prudent use of antibiotics. 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.

LIST OF PUBLICATIONS

Publications related to the Thesis

I. **Juhasz Z**, Benko R, Matuz M, Viola R, Soos G, Hajdu E: Treatment of acute cystitis in Hungary: Comparison with national guidelines and with disease-specific quality indicators. *Scand J Inf Dis.* 2013; 8:612-615. **IF:1,64**

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.

Abstracts related to the Thesis

I. **Juhász Zoltán**, Benkő Ria, Matuz Mária, Hajdú Edit: A húgyúti fertőzések epidemiológiai jellemzői az alapellátásban Csongrád megyében. In: A Magyar Infektológiai és Klinikai Mikrobiológiai Társaság 41. Kongresszusa. Szolnok, 2013. október 3-5. p. 38.

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III. Hajdú Edit, **Juhász Zoltán**, Benkő Ria, Matuz Mária, Soós Gyöngyvér: Antibiotikum kezelési gyakorlat a járóbeteg ellátásban acut cystitis esetén-értékelés európai minőségi indikátorok alkalmazásával. In: Magyar Belgyógyász Társaság 44. Nagygyűlése. *Magyar Belorvosi Archívum* 65:(6) p. 361 (2012)

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V. **Juhász Zoltán**, Matuz Mária, Benkő Ria, Biczók Zsuzsanna, Hajdú Edit, Soós Gyöngyvér: Antibiotic use in cystitis. *Clinical Microbilogy and Infection* 18:(s3) pp. 642-643. (2012)

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