

OUTPATIENT ANTIBIOTIC CONSUMPTION FOR URINARY INFECTIONS IN CROATIA 2005 - 2014: WHAT CAN BE LEARNED FROM UTILIZATION TRENDS

PORABA AMBULANTNO PREDPISANIH ANTIBIOTIKOV PRI OKUŽBAH SEČIL NA HRVAŠKEM MED LETI 2005 IN 2014: KAJ SE LAHKO NAUČIMO IZ TRENDOV PORABE

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ABSTRACT

Keywords:

antibiotics, utilisation trends, urinary tract infections, bacterial resistance

Aim: The aim of this study was to determine quantities of antibiotics used mainly or exclusively for urinary tract infections in Croatia between 2005 and 2014, to describe utilisation trends, and general consequences of antibiotic consumption on antimicrobial resistance.

Methods: Antibiotic utilisation data were obtained from annual reports of both the Croatian Drug Agency and Croatian Academy of Medical Sciences. Antibiotic consumption was expressed in DDD/1000 inhabitants/day (DDD TID). Antimicrobial resistance was analysed for *E. coli*, *E. faecalis*, *E. faecium*, *P. aeruginosa*, *Klebsiella* spp., *P. mirabilis*. Descriptive statistics were used to process data and calculate trends.

Results: Overall, utilisation of antibacterials decreased by 4.8% (from 3,35 to 3,19 DDD TID), while trends of individual agents varied substantially - from 87% decline for ceftibuten to 160% rise for levofloxacin. The consumption of quinolones increased by 32.3%. This was mostly due to increased ciprofloxacin consumption (144% raise). Sulfamethoxazole-trimethoprim declined by 57%, while nitrofurantoin increased by 86%. The use of fosfomycin was marginal. Antimicrobial resistance of *E. coli* increased against quinolones by 54.5%, and against nitrofurantoin by 2-3%. Quinolone resistance of other pathogens (*Klebsiella* spp, *Proteus mirabilis*), increased variably - between 17.2% (*Klebsiella*) and 90% (*Proteus*), while for *P. aeruginosa* remained the same at 22%.

Conclusion: High rates of antimicrobial utilisation require prescribing restrictions and educational interventions. The increased use of fluoroquinolones is a potentially serious public health threat due to the rapid development of resistance among uropathogens. This threat can be avoided by greater use of nitrofurantoin and fosfomycin.

IZVLEČEK

Ključne besede:

antibiotiki, trendi porabe, okužba sečil, odpornost bakterij

Cilj: Cilj te študije je ugotoviti količino antibiotikov, ki so bili porabljeni za okužbe sečil na Hrvaškem med leti 2005 in 2014 in prikazati trende porabe in njene posledice glede odpornosti mikrobov na zdravila.

Metode: Podatki o porabi antibiotikov izhajajo iz letnih poročil hrvaške agencije za zdravila in hrvaške akademije medicinskih znanosti. Poraba antibiotikov je izražena v obliki DDD/1000 prebivalcev/dan (DDD TID). Odpornost mikrobov na zdravila je analizirana za *E. coli*, *E. faecalis*, *E. faecium*, *P. aeruginosa*, *Klebsiella* spp., *P. mirabilis*. Za obdelavo podatkov in izračun trendov je uporabljena opisna statistika.

Rezultati: Splošna poraba antibiotikov se je zmanjšala za 4,8 % (iz 3,35 na 3,19 DDD TID), medtem ko so se trendi porabe posameznih zdravil občutno spreminjali - od upada v višini 87 % za ceftibuten do dviga za 160 % za levofloksacin. Poraba kinolonov se je zvišala za 32,3 % predvsem zaradi povišane porabe ciprofloksacina (dvig za 144 %). Poraba trimetoprim sulfametoksazola (kotrimoksazola) se je zmanjšala za 57 %, medtem ko se je poraba nitrofurantoina povišala za 86 %. Odpornost mikroba *E. coli* na kinolone se je zvišala za 54,5 %, na nitrofurantoin pa za 2-3 %. Odpornost na kinolone pri drugih patogenih (*Klebsiella* spp, *Proteus mirabilis*) se zvišuje spremenljivo, in sicer med 17,2 % (*Klebsiella*) in 90 % (*Proteus*), vrednost pa je ostala enaka pri patogenu *P. aeruginosa*, in sicer 22 %.

Zaključek: Visoka poraba antibiotikov zahteva omejitve predpisovanja zdravil in izobraževanje populacije. Zaradi hitrega razvoja odpornosti pri uropatogenih predstavlja povišana poraba fluorokinolonov grožnjo javnemu zdravju. Tej grožnji se lahko izognemo z večjo porabo nitrofurantoina in fosfomicina.

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1 INTRODUCTION

Urinary tract infections (UTIs) are a frequent occurrence in routine work of both family doctors and hospital specialists. They are the second most frequent indication for antibiotics, after respiratory infections. The predominant pathogens are *Escherichia coli* (75-90% of cases), *Staphylococcus saprofiticus* (5-15%), followed by *Proteus mirabilis*, *Klebsiella* spp i enterococci (1). The key principles in their management are knowledge of common pathogens, antimicrobial susceptibility and empirical choice of agents. Microbiological verification and susceptibility testing are performed mostly in situations of failure of initial therapy, or in complicated infections (2). International guidelines conclude that there is no a singular optimal regimen in management of uncomplicated urinary infections (2), and also that there is a need for the development of "double strategy" for virtually any antimicrobial indication: assessment of efficacy (pathogen eradication) together with minimizing the risk of collateral damage (induction of antibiotic resistance) (3). According to one study from primary care the prevalence of urinary infections in Croatia was 49.7/1000 in 2004, of which 38.2/1000 were uncomplicated cystitis (4). According to Croatian health statistics, there were 228 313 recorded cases of cystitis in family medicine offices in 2014 (out of 10 187 976 consultations/ visits/ prescriptions, or 2.24% of all encounters) (5).

In Croatia, treatment guidelines for urinary infection are developed by ISKRA (Interdisciplinary Section for Control of Antibiotic Resistance) in 2007, with an update in 2012 (6, 7). Prescription of all antibiotics in primary care is allowed without restrictions, except for ciprofloxacin. Its use is only allowed after recommendation of a hospital specialist, which is supported in ISKRA and the Croatian Institute for Health Insurance - CIHI recommendations (8). The effects of that restriction are questionable since norfloxacin is unrestrained and all fluoroquinolones induce cross-resistance (9, 10).

Antibiotic resistance surveillance in Croatia is performed by the Committee for Monitoring of Antibiotic Resistance of the Croatian Academy of Medical Sciences (CAMS), Public Health Department. Systematic surveillance of 16 most significant pathogens, from 30 microbiological laboratories across the country, began in 1996 (11-13). The sampling method included both inpatient and outpatient specimens. Resistance of *E.coli* in 2014 exceeded 20% for co-trimoxazole, 17% for ciprofloxacin, and 2% for nitrofurantoin. The proportion of *E. coli* strains producing extended-spectrum beta-lactamases (ESBL), was relatively low at only 2%. A sharp increase of ESBL strains has been recorded for *K. pneumoniae* - from 22% in 2006 to 32% in 2007, remaining at this level until now (12, 13).

Antibiotic prescribing practices vary across the EU countries (14). Since the pattern of prescribing has a major impact on the development and dissemination of resistance (15, 16), analysis of antibiotic utilisation trends in general, as well as of their specific subgroups, could provide valuable information in developing guidelines as well as in changing prescribing practice. The overall outpatient utilisation of antibiotics in Croatia was close to the European average in 2014 (21.4 defined daily doses per 1000 inhabitants, DDD TID), without greater fluctuations in the last five years (17). Due to the growth of resistance of *E. coli* against amoxicillin, oral cephalosporins, co-trimoxazole and fluoroquinolones, guidelines encourage the use of older antibiotics with a lower potential for the development of resistance: fosfomycin, nitrofurantoin and pivmecillinam (not registered in Croatia), in the course of 3 - 5 days. Each of them preserved over 90% efficiency against *E. coli*, nitrofurantoin even over 95%, despite decades in use (2, 18, 19). The ratio of older antimicrobials - nitrofurantoin and fosfomycin against all other subgroups (co-trimoxazole, beta-lactams, and fluoroquinolones) is of great importance as a potential predictor of national resistance trends. The aim of this study was (i) to analyse utilisation of antibiotics used mainly (among other indications) or exclusively for urinary tract infections in a ten-year period (2005-2014), (ii) to compare consumption trends between "low-resistance" antimicrobials (nitrofurantoin, fosfomycin) and others, especially fluoroquinolones, and to (iii) discuss the broad consequences of increasing antibiotic utilisation on advancement of antimicrobial resistance.

2 MATERIALS AND METHODS

This is observational study based on routinely collected data on the utilisation of antimicrobials for urinary infections, with emphasis to fluoroquinolones, and trends in antibiotic resistance, in a period from 2005-2014 for antibiotics, and 2007 - 2014 for resistance. Antibiotic consumption from the ATC group J01M (quinolones) and J01XE (nitrofurantoin derivatives, nitrofurantoin) was extracted from the annual reports of the Croatian Agency for Medicines (HALMED) (20). These HALMED reports display reimbursement data from the network of community and hospital pharmacies, expressed in DDD TID, while the Resistance Committee of the CAMS collected data from wholesale suppliers up to 2009, and reimbursement data from 2010 onward (12, 13). Although both sources provide information on antibiotic consumption, we have chosen HALMED as more reliable because of their method of data collection and the clear separation between outpatient and inpatient consumption. Only the utilisation of co-trimoxazole (in DDD TID) was extracted from the CAMS records, because it was expressed only in financial terms

in HALMED (12, 13). Antibiotics from beta-lactam group were omitted from more detailed analysis and calculation of trends due to their wide range of indications. However, since ISKRA guidelines recommend amoxicillin-clavulanic acid, cephalexin, cefuroxime, cefixime and ceftibuten as alternative drugs and in some cases as first-line agents (amoxicillin-clavulanic acid in uncomplicated pyelonephritis) (7), we have included their use in the discussion.

Resistance was expressed in percentages. The Resistance Committee of the CAMS surveilled samples from 30 microbiological laboratories countrywide, as well as from several bigger hospitals and university clinics, using EARSS-Net project methodology. Data obtained through this methodology are expressed as national resistance rates (population level of resistance) and used in guidelines as a predictor of clinical efficacy of complementary antibiotic groups (12, 13). Health statistics data of urinary infections, under ICD10 codes N30, were taken from the Croatian Health Statistics Yearbook, edition 2014 (5). The average annual increase for quinolones, co-trimoxazole and nitrofurantoin were calculated, and expressed in percentages. The annual prevalence of resistant pathogens (*E. coli*, *K. pneumoniae*, *P. mirabilis*, *P. aeruginosa*, *E. faecalis* and *E. faecium*), against beta-lactams, fluoroquinolones (ciprofloxacin, norfloxacin), co-trimoxazole and nitrofurantoin between 2007 - 2014 were expressed in percentages. Descriptive statistics and Microsoft Excel software were used to process data, calculate trends and create tables and graphs.

3 RESULTS

The outpatient consumption of fluoroquinolones was between 85 and 90% of the total and of co-trimoxazole between 93 and 95%. The overall quinolone consumption increased by 32.3%, or from 1.27 DDD TID in 2005, to 1.68 DDD TID in 2014. Norfloxacin utilisation in 2005 was 0.95 DDD TID or almost four times that of ciprofloxacin (0.25 DDD TID), but decreased to 0.86 DDD TID in 2014, while ciprofloxacin increased by the rate of 144% (14% annually) to 0.61 DDD TID. The use of levofloxacin, registered in 2012, increased from 0 to 0.13 DDD TID in just two years, while the moxifloxacin remained at 0.08 DDD TID (Table 1). There was a disproportionately high increase of norfloxacin in 2006 (from 0.95 DDD TID to 1.25 DDD TID, or by 31.6%), followed by a decrease in 2007, to 0.8 DDD TID, with a later moderate drop of utilisation rate. Ciprofloxacin showed, contrary to this, a balanced increasing trend (Table 1).

Table 1. Utilisation of quinolones, co-trimoxazole and nitrofurantoin in Croatia, 2005 - 2014, according to HALMED (DDD TID).

| | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | % of change |
|------------------------|------|------|------|------|------|------|------|------|------|------|-------------|
| QUINOLONES | | | | | | | | | | | |
| ciprofloxacin | 0.25 | 0.41 | 0.45 | 0.47 | 0.58 | 0.59 | 0.59 | 0.55 | 0.59 | 0.61 | 144 |
| pefloxacin | 0.01 | 0.01 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| norfloxacin | 0.95 | 1.25 | 0.8 | 0.81 | 0.77 | 0.8 | 0.7 | 0.77 | 0.83 | 0.86 | -9.37 |
| levofloxacin | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.05 | 0.13 | 0.13 | |
| moxifloxacin | 0.07 | 1.1 | 0.08 | 0.12 | 0.12 | 0.12 | 0.11 | 0.1 | 0.09 | 0.08 | |
| tot quinol | 1.27 | 1.76 | 1.34 | 1.41 | 1.47 | 1.52 | 1.39 | 1.47 | 1.63 | 1.68 | 32.28 |
| CO- TRIMOXAZOLE | | | | | | | | | | | |
| Outpatient DDD | 1.57 | 1.35 | 1.4 | 1.17 | 0.98 | 0.87 | 0.73 | 0.72 | 0.67 | 0.66 | |
| Hospital DDD | 0.08 | 0.07 | 0.07 | 0.06 | 0.06 | 0.05 | 0.05 | 0.06 | 0.04 | 0.05 | |
| Total DDD | 1.65 | 1.42 | 1.47 | 1.23 | 1.04 | 0.92 | 0.78 | 0.78 | 0.71 | 0.71 | -57 |
| HRK | 4.32 | 5.3 | 3.9 | 9.89 | 3.53 | 3.23 | 2.68 | 2.46 | 2.55 | 2.45 | |
| NITROFURANTOIN | | | | | | | | | | | |
| nitrofurantoin | 0.43 | 0.65 | 0.37 | 0.6 | 0.69 | 0.66 | 0.68 | 0.7 | 0.75 | 0.8 | 86.05 |

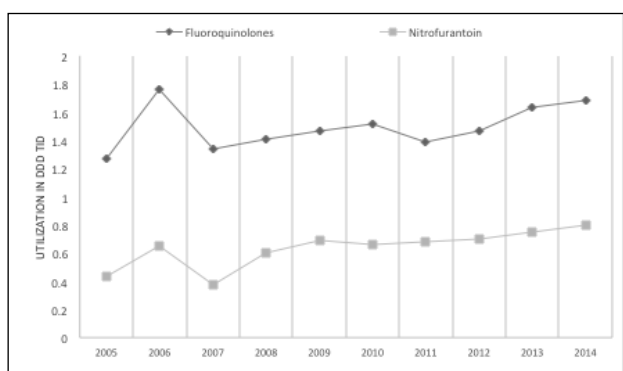


Figure 1. Utilisation of quinolones and nitrofurantoin in Croatia, 2004 - 2015 (DDD TID).

The consumption of nitrofurantoin almost doubled - from 0.43 DDD TID in 2005 to 0.80 DDD TID in 2014, or by 8.6% annually. Its use approached that of co-trimoxazole, and even slightly exceeded (0.71 DDD TID in 2014) (Table 1, Figure 1). Consumption trends of all four antibiotics converged in 2014 toward roughly equal volumes (norfloxacin 0.86, ciprofloxacin 0.61, co-trimoxazole, and nitrofurantoin 0.80 DDD TID) (Figure 2). In 2007 nitrofurantoin suddenly dropped from 0.65 DDD to 0.37 DDD TID (43%), and then recovered to 0.6 DDD TID in 2008 onwards (Figure 2).

The use of co-trimoxazole steadily decreased from 1.65 DDD TID in 2005 to 0.71 DDD TID in 2014 (Table 1, Figure 2). In HALMED reports, the utilisation of beta lactams (in DDD TID) were as follows: amoxicillin-clavulanic acid 8.65, cephalixin 0.85, cefuroxime 1.68, cefixime 0.18 and ceftibuten 0.03 (2014).

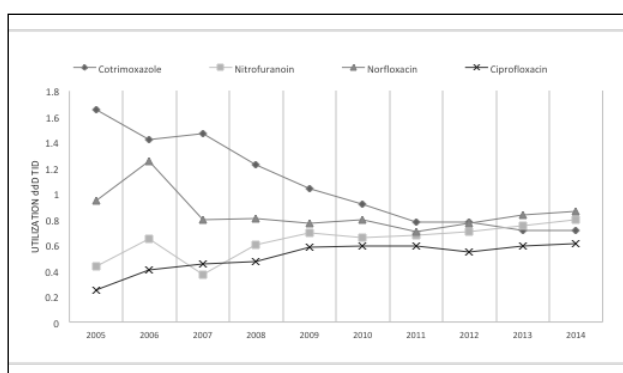


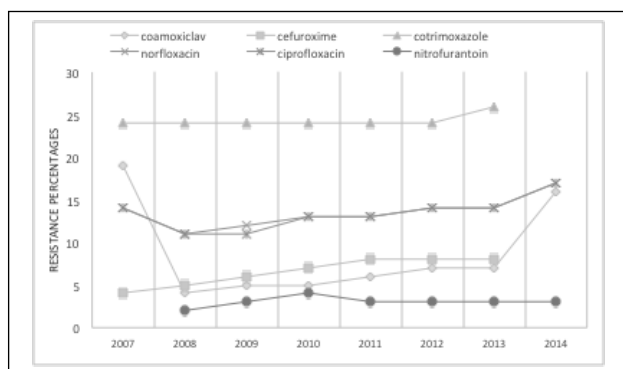
Figure 2. Utilisation of co-trimoxazole, nitrofurantoin, norfloxacin and ciprofloxacin in Croatia, 2005 - 2014 (DDD / TID).

Antibiotic resistance increased against all standard therapeutic agents, but disproportionately and with great variations between individual drugs, during the eight-year period (Table 2). The resistance of *E. coli* increased sharply to amoxicillin-clavulanic acid - from 4% in 2008 to 16% in 2014 (Table 2, Figure 3), for cefixime from 3%-7%, and for cefuroxime from 4%-8%. In 2014 the resistance of *E. coli* to cephalixin and cefuroxime was between 8-10%, to cefixime and ceftibuten between 4% and 6%. There was a high level of insusceptibility to co-trimoxazole (24%), which increased to 26% in 2014, while resistance to both fluoroquinolones (ciprofloxacin and norfloxacin) advanced from 12% in 2007 to 17% in 2014, or by 54.5% (Table 2, Figures 3 and 4).

Resistance of *K. pneumoniae* increased mostly to amoxicillin-clavulanic acid (94.4%), from 18% of isolates in 2008 to 35% in 2014. Insusceptibility to cephalosporins was between 35% and 39% (cefuroxime 39%, cephalixin 39%, cefixime 35%), and for co-trimoxazole and nitrofurantoin at 36-37%. Resistance to norfloxacin and ciprofloxacin increased, as in the case of *E. coli*, from 29% in 2008 to 34% in 2014, or by 17.2%. *P. mirabilis* strains resistant to cephalosporins increased between 35.7% (cefuroxime) and 54.4% (cefixime), for amoxicillin-clavulanic acid by 38.4%, while for norfloxacin and ciprofloxacin upsurged by 90% - from 11% to 21% (Table 2). The resistance of *P. aeruginosa* to norfloxacin and ciprofloxacin was between 23-25%, without greater changes. *E. faecalis* preserved good susceptibility to amoxicillin and nitrofurantoin, while in 2014 it became highly resistant to quinolones (21%). Resistance patterns of *E. faecium* were similar to *P. aeruginosa* (Table 2).

Table 2. Resistance of main uropathogens in Croatia, 2007 - 2014 (in %).

| | 2007 | | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 |
|----------------------------|----------|-----------|------|------|------|------|------|------|------|
| | hospital | community | | | | | | | |
| <i>E. coli</i> | | | | | | | | | |
| co-amoxiclav | 15 | 19 | 4 | 5 | 5 | 6 | 7 | 7 | 16 |
| cefuroxime | | | 4 | 5 | 6 | 7 | 8 | 8 | 8 |
| cotrimoxazole | | | 24 | 24 | 24 | 24 | 24 | 24 | 26 |
| norfloxacin | 12 | 14 | 11 | 12 | 13 | 13 | 14 | 14 | 17 |
| ciprofloxacin | 12 | 14 | 11 | 11 | 13 | 13 | 14 | 14 | 17 |
| nitrofurantoin | | | 2 | 3 | 4 | 3 | 3 | 3 | 3 |
| <i>Klebsiella p</i> | | | | | | | | | |
| co-amoxiclav | | | 18 | 21 | 21 | 28 | 26 | 25 | 35 |
| cefuroxime | | | | 35 | 37 | 40 | 39 | 37 | 39 |
| cotrimoxazole | | | 36 | 40 | 37 | 40 | 41 | 36 | 37 |
| norfloxacin | | | 29 | 32 | 31 | 34 | 35 | 32 | 34 |
| ciprofloxacin | | | 29 | 32 | 30 | 33 | 34 | 31 | 34 |
| nitrofurantoin | | | 35 | 37 | 36 | | | | |
| <i>Proteus m</i> | | | | | | | | | |
| co-amoxiclav | | | 13 | 13 | 16 | 16 | 19 | 18 | 18 |
| cefuroxime | | | | 14 | 17 | 17 | 20 | 20 | 19 |
| cotrimoxazole | | | 35 | 35 | 38 | 36 | 38 | 38 | 36 |
| norfloxacin | | | 12 | 14 | 16 | 17 | 21 | 21 | 21 |
| ciprofloxacin | | | 11 | 13 | 16 | 17 | 20 | 20 | 21 |
| nitrofurantoin | | | 97 | 98 | 97 | 100 | 100 | 100 | 100 |
| <i>Pseudomonas</i> | | | | | | | | | |
| gentamicin | | | 29 | 28 | 28 | 27 | 28 | 26 | 23 |
| norfloxacin | | | 24 | 25 | 23 | | | | |
| ciprofloxacin | | | 24 | 24 | 22 | 24 | 24 | 23 | 22 |
| <i>E. faecalis</i> | | | | | | | | | |
| nitrofurantoin | | | 1 | 1 | 1 | 1 | 1 | 1 | 0 |
| norfloxacin | | | | | | | | | 21 |
| <i>E. faecium</i> | | | | | | | | | |
| nitrofurantoin | | | 34 | 40 | 23 | | | | |
| norfloxacin | | | | | | | | | 80 |

**Figure 3.** *E. coli* isolates resistant to amoxicillin-clavulanic acid, co-trimoxazole, ciprofloxacin, norfloxacin and nitrofurantoin, in Croatia, 2008 - 2014.

The antimicrobial resistance against ciprofloxacin was relatively stable during a seven-year period. There were 25-30% resistant strains of *K. pneumoniae* and *P. aeruginosa*, and 10-15% of *E. coli* and *P. mirabilis*. Resistance of *E. coli* and *P. mirabilis* increased to 17% and 21% in 2014. Both norfloxacin and ciprofloxacin had an equal percentage of resistant uropathogens (*E. coli*, *K. pneumoniae* and *P. mirabilis*) (Table 2, Figure 4).

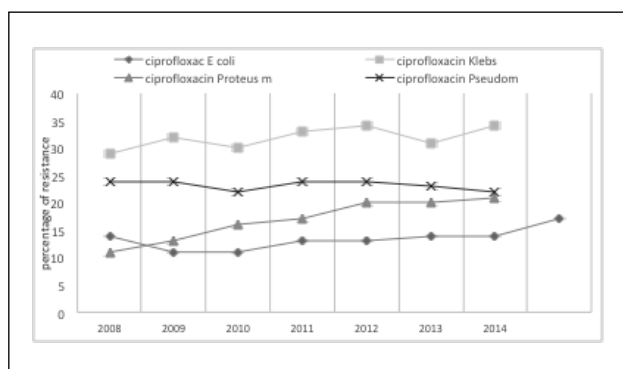


Figure 4. Resistant isolates of main uropathogens to ciprofloxacin, in Croatia, 2008 - 2014.

4 DISCUSSION

There is very little research in Croatia about the actual prevalence of urinary infections in primary care. The figure from health statistics of 2.24% of UTI diagnoses out of all registered health encounters (5), although relatively imprecise, still provides some impression on their public health burden. In the USA, from 1997-2003, more than 8 million primary care visits associated with UTI were recorded (21). The estimated annual costs for their treatment exceeded 3.5 billion USD (21). In a hospital setting they represent between 12.9 and 19% of the total hospital infections (22).

Management of urinary infections has become a therapeutic challenge because of rapid dissemination of antimicrobial resistance. Due to variable prevalence of resistant strains, as well as differences in antibiotic prescribing practice among EU countries, different recommendations for empirical antibacterials are present in guidelines (23). ISKRA guidelines, developed by a multidisciplinary team in 2007 and updated in 2012, are still a reliable model for empirical treatment of urinary infections in primary care (6). However, they differ from some international guidelines in classification of urinary infections (5 groups of urinary infections versus 3 groups), and choice of first line antibiotics (omitting of co-trimoxazole) (2, 24).

For uncomplicated UTIs in women drug of choice is either nitrofurantoin, 100 mg every 12 hours per dose, for 7 days, or fosfomycin 1x3 grams, one dose (7). Nitrofurantoin, in use for almost 65 years, is a first choice for both women's and men's UTIs due to its low potential for the development of resistance (25, 26), and triple mechanism of action (27, 28). The macrocrystalline 50 mg form (the only available in Croatia) requires dosing every 6 hours, while the dosing of macrocrystalline-monohydrate 100 mg form is every 12 hours. However, guidelines (7, 29), recommend 12 hour-dosing, which is apparently suboptimal. This drug is of great importance,

apart from uncomplicated cystitis, in catheter-associated infections. In catheterized hospitalized patients with bacteriuria the most common pathogens are *E. coli* or Enterococci, and nitrofurantoin retained its efficacy for years (25, 26), even against vancomycin-resistant strains (VRE). A 68% growth of its consumption and 0.8 DDD TID in 2014 is encouraging (Table 1), because it reflects a positive change in prescribing practice of family doctors. According to the ESAC-Net database, nitrofurantoin use (2014) in some neighbouring countries was as follows: 0.26 DDD TID in Austria, 0.25 DDD in Slovenia and 0.19 DDD in Hungary (30). Prescribing of fosfomycin (registered in Croatia in 2012) was marginal: in 2013 - 7 packages, in 2014 - 50 packages (20). Its use is difficult to compare between countries because of classification in ATC group with 10 other drugs (31).

The two most represented quinolones: norfloxacin and ciprofloxacin dominated in prescribing practice for UTIs in 2014, with 1.47 DDD TID (Table 1). Together, they were prescribed almost twice as much as co-trimoxazole (0.71 DDD TID) or nitrofurantoin (0.80 DDD TID). The ratio of utilisation volumes between quinolones and nitrofurantoin decreased from 2.8:1 in 2004 to 1.8:1 in 2014, which is definitely a positive phenomenon. But, despite that, ciprofloxacin annual utilisation has been increasing 14% between 2005 and 2014. If we consider that this medicine may only be prescribed by the judgment of hospital specialists, it is difficult to explain such an upswing. Norfloxacin was prescribed at 0.86 DDD TID, nitrofurantoin in 0.80 DDD TID, that is the alternative drug and is more frequent than the first-line drug (Table 1). Given that ISKRA guidelines recommend norfloxacin only as an alternative in uncomplicated cystitis in women, it is clear that the use of both quinolones has come out of scope of guidelines. In addition to that, norfloxacin is less potent in vitro than ciprofloxacin against gram negative bacteria in general (32). Ciprofloxacin, a "reserve" drug for UTIs in men and pyelonephritis, is rapidly approaching the consumption of norfloxacin and nitrofurantoin (Table 1). Restrictions in use, proposed by CIHI and ISKRA guidelines, to reduce overutilisation and preserve efficacy, generally failed to achieve this aim: its use increased almost 4.5 times faster than all other quinolones - from 0.25 DDD TID in 2005 to 0.61, or by 144% (Table 1, Figure 1). A similar trend was documented in Austria: from 1998 - 2007 ciprofloxacin use increased by 118.9% (33). However, data from HALMED (increase in quinolone use from 1.27 to 1.68 DDD TID) are different from the ESAC Net (decrease in quinolone use from 1.60 to 1.50 DDD TID) (30) probably because of differences in assembling, as described in the methods. Among the ESAC participating countries the overall quinolone consumption in 2014 was 1.30 DDD TID in Austria, 1.11 DDD in Slovenia and 2.41 DDD in Hungary (30). From countries that did not participate in the ESAC project total consumption

(in 2011) was 4.4 DDD TID in Montenegro, 2.5 DDD in Serbia, and only 0.75 DDD in Azerbaijan (34). However, we do not know the proportion used for urinary infections only. In Switzerland quinolones were prescribed to 37.2% of women with urinary infections, far more than the recommended maximum of 5% (35).

Overutilisation of quinolones probably contributed to increase of fluoroquinolone resistance on a country level (54% rise for *E. coli* and 90% for *P. mirabilis*) (Table 2). It is important to note that the potential for resistance of both norfloxacin and ciprofloxacin is virtually equal (9, 10). The frequency of quinolone-resistant *E. coli* was 17% in 2014, and further advancement will probably soon reach the threshold of 20%, when both of them become clinically inefficient, according to IDSA guidelines (2). Fluoroquinolone resistance is of particular clinical importance because of the close connection with ESBL production in gram-negative pathogens (36). The range of quinolone-resistant isolates in uncomplicated community acquired infections (CA-UTIs) varied from 10% in ESBL negative strains to 70% in ESBL positive strains, extending up to 90% in complicated CA-UTIs (37). Previous fluoroquinolone use was an important risk factor for the acquisition of ESBL-producing *E. coli* in non-hospitalized patients with uncomplicated UTIs (38, 39).

It is difficult to estimate beta lactam utilisation in urinary infections due to their overlap with other indications (respiratory and other). However, in 2014 their use was substantial: amoxicillin-clavulanic acid (8.65 DDD TID) surpassed fluoroquinolones (1.47 DDD TID), by almost 6:1, and cefuroxime (1.68 DDD TID) by 1:0.9. In European urological guidelines cephalosporins are not mentioned; not even as a second choice in uncomplicated cystitis (24), while in ISKRA guidelines they are simply second choices in both cystitis and pyelonephritis, thus giving false impression of their equal efficacy in all clinical scenarios (7). Resistance, however, threatens to eliminate all three generations of oral cephalosporins. Insusceptibility of *E. coli*, although relatively low at present (ceftibuten 5%, cefixime 7%, cefuroxime 8%, in 2014), progress at rates of between 66 and 133% (Table 2). Co-trimoxazole declined by 57% in ten years - to 0.66 DDD TID (Table 1), and this change is probably justified due to a high prevalence of resistant strains in 2014: *E. coli* 26%, *K. pneumoniae* 37%, *P. mirabilis* 36%, *P. aeruginosa* 100% (Table 2). Its use varied considerably between individual countries: from 0.07 DDD TID in Austria (2014), and 0.19 DDD in Slovenia, to 0.50 DDD in Hungary (30).

Urinary infections in children are also frequent in primary care, with 9180 recorded cases of cystitis (up to 6 years), in 2014 (5). In the UK their prevalence is 3.6% for boys, and 11% for girls (40). The spectrum of oral antibiotics is limited to beta-lactams, co-trimoxazole and nitrofurantoin, because fluoroquinolones are not registered for children

under 14 years, and fosfomycin for children under 6 years (41). Nitrofurantoin is a first choice for children too (42). Due to unavailability of suspension in Croatian market, it can be applied as an ex-temporaneous formulation. Urinary infections in men are classified as complicated in most guidelines. While some guidelines advise ciprofloxacin (2, 24), other recommend trimethoprim and nitrofurantoin as a first choice, and performing urinary culture in case of failure (43).

5 STRENGTHS AND LIMITATIONS

The main strength of this study is the use of data on the consumption of antibiotics from the HALMED database, which collects information from public pharmacies (for the outpatient sector), and clearly separate inpatient from outpatient sources from the beginning of systematic surveillance. Also, the observational period is long enough to draw conclusions on trends on antibiotic consumption and to compare the obtained data with those in international publications. There are several limitations: national resistance rates shown in the CAMS reports do not separate hospital from outpatient samples. Secondly, antimicrobial resistance is induced by many antibiotics - the overuse of "respiratory" antimicrobials is also reflected in the resistance of urinary pathogens. Finally, many antibiotics, especially beta-lactams, are indicated for infections other than urinary. Also, the information from HALMED database does not allow visibility of the actual application of specific antibiotic groups.

6 CONCLUSIONS

Utilisation of antimicrobials for UTIs in Croatia is characterized with a high proportion of fluoroquinolones (norfloxacin and ciprofloxacin) compared to older agents - nitrofurantoin and fosfomycin, which retained excellent efficacy for most gram-negative urinary pathogens, despite more than five decades of being in use. Prescribing restrictions imposed on ciprofloxacin were basically inefficient. The utilisation rapidly increased instead of being under control. Overutilisation of both ciprofloxacin and norfloxacin represents an important public health hazard, due to their powerful impact on induction and advancement of resistance, while underutilisation of nitrofurantoin and fosfomycin by family doctors requires clarification in further research.

Medicine today fights a grim battle with resistant bacteria, and its outcome decides on the very essence of our profession and even on human society as a whole. Family doctors, being on the first line of healthcare, need freedom in their clinical decisions, as well as clear and unambiguous rules, and not administrative measures.

The essential advice in management of UTIs in primary care should be “keep it simple” (44) - or make treatment decisions based on simplest diagnostic tests: symptom score, nitrites and leukocyturia, avoid treatment of asymptomatic bacteriuria (except in pregnancy), and always prescribe nitrofurantoin or fosfomycin first, only when and if necessary.

AUTHOR CONTRIBUTION

Both authors contributed equally to the work described in the manuscript.

CONFLICTS OF INTEREST

The authors declare that no conflicts of interest exist.

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ETHICAL APPROVAL

Estimated as unnecessary from the Ethical Committee because of the absence of human subjects.

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