Differences in prescribing antibiotics for urinary tract infections: a cross-sectional study among general practitioners in Croatia

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Abstract

Background

The spread of multidrug-resistant urinary pathogens in the outpatient setting requires strict adherence in prescribing the first-line antibiotics. We aimed to analyze the utilization of antibiotics for urinary tract infections (UTIs) in a sample of general practitioners (GPs) in uncomplicated and complicated infections together, and independently for uncomplicated lower urinary tract infections (uLUTIs) in women over 18 years. Prescribing of the first-line antimicrobials and fluoroquinolones was compared with the European Surveillance of Antimicrobial Consumption (ESAC) quality indicators.

Methods

A cross sectional study on a sample of 42 GPs from all over Croatia was conducted between 1th March to 31th October 2019. Prescriptions related to diagnoses of UTIs were collected from electronic medical records, on a monthly basis, and consumption expressed in the absolute number of prescriptions and prescription rates per 100 patients. Additionally, the percentage of antibiotics for UTIs compared to the overall antibiotic consumption for systemic use and the relationship between clinical experience and specialization with the prescribing rates were analyzed.

Results

Out of 24,117 prescriptions of all antibiotics for systemic use (ATC J01), 22% were issued for both complicated and uncomplicated urinary infections in both sexes, and 14.8% for acute cystitis in women over 18 years of age. The prescription rates per 100 patients were 37,5/100 for antibiotics for systemic use, 7,9/100 for antibiotics in all UTIs and 5,3/100 for uLUTIs. Large differences between the highest and lowest prescribing rates/ 100 patients (6 times) have been recorded, not related to the number of patients in care. Prescribing rates did not differ significantly with regard to length of service and specialization. Most physicians prescribed outside the recommended ranges according to ESAC prescribing quality indicators.

Conclusion

Empirical treatment of UTIs in a sample of GPs was suboptimal regarding quality criteria. Large individual differences in the prescriptive practice were not related to the number of patients in care, but occurred probably due to incorrectly adopted prescriptive habits.

Introduction

Uncomplicated LUTIs are one of the most common bacterial infections in women and one of the most common reasons for prescribing of antibiotics in primary care (1). On average, one in 10 women of all ages has at least one episode of acute cystitis per year, or 60% have at least one episode during their lifetime. The peak incidence is observed in young, sexually active women between 18 and 24 years of age (2). Most of these infections are treated in primary care. Antimicrobial guidelines in the last decade have consistently promoted the concept of first-line antibiotics (nitrofurantoin, fosfomycin, co-trimoxazole) in the empirical treatment of acute cystitis, based on their low potential for the development of resistance (3).

Prescribing of antibiotics for UTIs varies considerably among countries (4–6) which, with disproportionately high proportions of cephalosporins and fluoroquinolones, significantly influences undesirable trends in resistance. The growing prevalence of multidrug-resistant Enterobacteriaceae in primary care (7–8) necessitates the prompt and effective control over the utilization of fluoroquinolones and cephalosporins in the outpatient treatment of urinary infections (9).

Nitrofurantoin, and to a lesser extent fosfomycin, as first-line antibiotics in almost all current guidelines, are reliable and efficient in eradicating resistant pathogens (10–11). One of the basic preconditions in controlling the spread of resistance is the harmonization of antibiotic prescribing according to the guidelines for the specific infections in the outpatient setting. Croatian guidelines for the treatment of urinary tract infections were published in 2007 and 2014 (second version) (12). The first-line drugs for uLUTIs are in these guidelines only two: nitrofurantoin and fosfomycin, while co-amoxiclav, cephalexin, cefuroxime, cefixime, and norfloxacin were alternatives, depending on bacterial susceptibility.

Many studies have shown differences in the antibiotic selection and duration of therapy, as well as fluctuations in the degree of compliance with the guideline recommendations, ranging between 25–100% (13–14). Studies investigating prescribing practice of GPs in UTIs in Croatia are scarce. Extensive research by Škerk et al in 2009, although without the main goal of investigating compliance with prescribing guidelines, still demonstrated a relatively low level of appropriate use (15), while a recent study on the impact of guidelines on antibiotic prescribing in primary care found a positive change towards the use of nitrofurantoin compared to norfloxacin in 2019 (16). According to data from the Croatian Agency for Medicinal Products (HALMED), in 2018 the consumption of fluoroquinolones on an annual level exceeded the consumption of first-line antibiotics: 1.48 defined daily doses/1000 inhabitants/day (DDD TID) of fluoroquinolones (norfloxacin and ciprofloxacin), compared to 1.38 DDD TID of first-line antibiotics (17). In Croatia, the resistance of *E. coli* to fluoroquinolones from 2015 to 2020 varied between 18 and 20%, and to co-trimoxazole 26–27% (18).

Most of research on the rational prescribing of antibiotics is based on comparison with national guidelines or the ESAC quality indicators. The ESAC indicators of outpatient antimicrobial prescribing were developed to assess the appropriateness of antimicrobial utilization in the 6 most common infectious syndromes in primary care (19). The main goals of our study were i) to get an insight into the total consumption of antibiotics for systemic use and the proportion of antibiotics for UTIs), ii) to analyze the prescribing for uLUTIs especially regarding to the first-line drugs and alternative antibiotics, and iii) to assess of the compatibility of prescribing according to the ESAC quality indicators.

Methods

This is an observational prospective study conducted on a sample of 42 GPs from all over Croatia, regardless of completed specialization in family medicine, length or place of work. The main inclusion criterion was continuous work in the office for more than one year. Exclusion criteria were absence from work for more than two months. All GPs who accepted the participation met the main inclusion criterion, and none had interruptions throughout the study. Basic information about the purpose of the research and the invitation to participate as well as detailed instructions on the data collection were given by e-mail.

The study lasted 8 months – from 1st March to 31st October 2019. GPs were required to record, during their routine work, all visits related to UTIs in electronic medical records. They recorded all prescriptions related to the International Classification of Diseases, 10th revision (ICD10) codes from N10 to N49, in both sexes and in all age groups. Pregnant women were the only excluded category, because of being under care of primary gynecologists. Upon completion of collection process, prescriptions related to diagnoses of uLUTIs in women over 18 years of age (N30 - N30.9) were singled out from the initial set of data. Ten antibiotics were linked with diagnoses of UTIs: nitrofurantoin, fosfomycin, co-trimoxazole, amoxicillin-clavulanic acid, norfloxacin, ciprofloxacin, cefuroxime, cephalexin, cefixime and cefpodoxime. Repeated prescribing on the same patient was documented as two separate prescriptions.

Each GP has been assigned an identification code to hide personal information. They dispatched data once a month, incorporated in monthly reports. Antimicrobial consumption was expressed by the number of prescriptions and the rate of prescriptions per 100 patients. Appropriateness of prescribing was assessed by the ESAC quality indicators.

Statistics

Statistical analyses were performed using MaxStat Pro 3.6, MaxStat Software. In the description of numerical variables, standard measures of central tendency and dispersion were used - medians, quartiles, and interquartile ranges. Prescription of antibiotics, in absolute numbers and rates per 100 patients, were presented in tables and diagrams. The relationship between the number of prescriptions per 100 patients and years in service and completed specialization was analyzed by the Mann Whitney U test for independent samples.

Results

The GPs in the sample provided for a population of 67,547. The relatively low proportion of preschool children up to 7 years of age (1.1%) is explained by the practice of enrolling children on the lists of primary pediatricians in urban areas. Most GP teams had between 1,300 and 1,900 patients (median: 1,652) under care. A total of 24,117 prescriptions of all antibiotics for systemic use (ATC J01) were issued during the 8 months of follow-up, of which 5,317 antibiotics for all UTIs together (22%) and 3,581 (14.8%) prescriptions for uLUTIs in women over 18 years. The prescribing rates per 100 patients were 37,5/100 for all systemic antibiotics, 7,9/100 for all UTIs, and 5,3/100 for uLUTIs.

Table 1
Antibiotic utilization according to the absolute number of prescriptions and prescribing rates per 100 patients

	Population	**Antibiotics total ***		**Antibiotics UTIs total****		**Antibiotics for acute cystitis*****				
						Total		First-line	Quinolones	Beta-lactams
	n	n	n/100	n	n/100	n	n/100			
SUM	67 547	24 117		5317		3581		1852	642	1087
MIN	720	138	2.64	26	2.64	14	1.94	3	0	1
MAX	2072	1418	14.6	266	14.6	190	11.82	116	43	104
MEDIAN	1652	571.5	7.68	117	7.68	80	4.9	44	15	23
CI95%		565.97-577.03		115.87-118.13		79.23–80.77		43.57–44.43	14.85–15.15	22.78–23.22
Q1	1397.5	328.25		88.75		58.25		33	5.75	13.75
Q3	1819.25	766.25		156		107.75		56.25	21	34
IQR	421.75	438		67.25		49.5		23.25	15.25	20.25

*ATC J01, antibiotics for systemic use, all indications

**ICD10 code N10 – N40, all age groups, both genders

***ICD10 code N30 – N30.9, acute cystitis in women over 18 years

Out of the total number of antibiotics for UTIs, 67.3% were prescribed for uLUTIs. Table 1 shows significant individual variations in the number of prescriptions for all UTIs together, in both men and women, and for uLUTIs in women over 18 years as well. There was a 10 times difference between the highest and lowest number of prescriptions for all UTIs, and 13 times for uLUTIs, while the range between the highest and the lowest number of enlisted patients was only 2.9 times. To minimize the impact of the list size, antibiotic consumption was also expressed as the number of prescriptions per 100 patients (Table 1). The differences between rates per 100 patients for all UTIs (2.64/100 – 14.6/100) and for uLUTIs (1.94/100–11.82/100) were somewhat smaller: about 6 times in both cases.

Table 2
Distribution of GP teams according to prescription rates per 100 patients and proportion of antibiotics for UTIs in the total antibiotic utilization

PRESCRIPTION RATES/100 PATIENTS			
Prescriptions/100	UTIs total	Acute cystitis	
patients	n (%)	n (%)	
< 5/100	8 (19)	22 (52.4)	
5–10/100	25 (59.5)	18 (42.8)	
> 10/100	9 (21.4)	2 (4.7)	
PROPORTION OF ANTIBIOTICS FOR UTIs			
Proportion of antibiotics	GP teams	Prescriptions of antibiotics	
for UTIs	n (%)	Systemic use	UTIs
		n (%)	n (%)
> 30%	12 (28,6)	4092 (17)	1491 (28)
20–30%	14 (33,3)	8466 (35,1)	1959 (36.8)
10–20%	14 (33,3)	10216 (47,6)	1766 (33.2)
< 10%	2 (4,7)	3341 (13,8)	101 (1.9)
total		24117 (100)	5317 (100)

Most physicians prescribed at the rate of 5–10 prescriptions/100 patients for all UTIs and less than 5 prescriptions/100 for uLUTIs (Table 2). The highest rates were recorded in only two teams: team5 (all UTIs 14.6/100, uLUTIs 11.23/100) with 1541 patients on the list, and team40 (11.7/100–11. 82/100) with 1608 patients on the list.

The proportion of antibiotics for all UTIs among antibiotics for systemic use (all indications) also varied considerably. Most of GPs prescribed between 10% and 30% of all antibiotics for UTIs (Table 2). Here, the number of patients in care did not play a significant role either, because four physicians with a 40% and a higher percentage (team22 almost 50%) had a list size near the median of the sample (1652). Two GPs distinguished themselves with low proportions of less than 10% of urinary antibiotics: team10: 2006 patients, 6.6% and team12: 1335 patients, 9%, despite relatively large list sizes. The range between the highest and the lowest proportion of antibiotics for UTIs in the total utilization was about 7 times.

For uLUTIs in women over 18 years, GPs prescribed 51.7% of first-line antibiotics, 7.9% of fluoroquinolones, and 30.3% of beta-lactams (predominantly co-amoxiclav and cefuroxime) (Table 1). Among the first-line antibiotics, 31% were issued for nitrofurantoin, 12.65% for fosfomycin, and only 8% for co-trimoxazole. The ranges between the minimal and maximal number of prescriptions in these subgroups are significantly higher (38 times for the first-line antibiotics) than in the segment of all UTIs (Table 1). For this reason, a comparison with the ESAC quality indicators was considered more appropriate than a comparison between individual physicians. Indicator "a" was, due to the data collection method, 100%. Indicator “b” (proportion of patients over 18 years with cystitis/ other UTI prescribed the recommended antibiotic, acceptable range 80–100%) was achieved by only one physician (team20), while most teams (72.7%) used first-line antibiotics less than in recommended amounts. Almost one in four GPs in the sample used first-line drugs well below the recommended ranges (Table 3). Indicator "c" (proportion of patients over 18 with cystitis/ other UTI with prescribed fluoroquinolone, acceptable range 0–5%) reached just 5 teams. Almost all GPs (88%) prescribed well above the recommended range.

Table 3
Distribution of GP teams according to the ESAC quality indicators (QI)

	First-line antibiotics			Fluoroquinolones		
ESAC QI	≥ 80%	50–80%	≤ 50%	< 5%	5–20%	> 20%
teams	1	25	16	5	19	18
prescriptions (n)	50	1347	455	12	221	409
prescriptions (%)	2.70%	72.70%	24.50%	1.90%	34.40%	63.40%

The prescribing rates per 100 patients in uLUTIs according to the years in service and completed specialization are shown in Table 4. The sample was divided into two groups (up to 15 years in service and over). The association of each of the categories (i.e., clinical experience and completed specialization) with the number of prescriptions/100 patients was examined by the Mann-Whitney U for independent samples, and the results (P values) are shown in the tables.

Table 4
Results of the Mann-Whitney U test for prescribing rates/100 in uLUTIs according to the length of service and completed specialization

Years in service	GPs	Antibiotics total	Antibiotics first line	Quinolones	
(years)		(prescript/100)	(prescript/100)	(prescript/100)	
< 15	25	4.85/100	2.41/100	0.82/100	
15 ≥	17	5.93/100	3.2/100	1.12/100	
median age group < 15					2.41/100
median age group ≥ 15					3.2/100
median difference					-0.79/100
P-value					0.51
Specialization	GPs	Antibiotics total	Antibiotics first line	Quinolones	
		(prescript/100)	(prescript/100)	(prescript/100)	
yes	26	5.79	2.94	1	
no	16	4.45	2.39	0.85	
median specialization					2.94
median without specialization					2.39
median difference					0.55
P-value					0.512

The P-value was below the statistical significance (P = 0.51, U = 6, U´ = 3) for both groups of the length of work. The median rate per 100 patients for the group with less than 15 years of service was 2.41/100 and for the second group 3.2/100. The two groups, therefore, did not differ in the total number of prescriptions for uLUTIs, as well as in the first-line antibiotics and fluoroquinolones. Similar results were observed regarding specialization. There was no statistically significant distinction between the completed specialization and prescribing rates/100 both for the total number of prescriptions in uLUTIs, and prescriptions of first-line agents and quinolones (Table 4.).

Discussion

Significant individual differences were observed among GPs regarding the number of prescriptions, prescribing rates per 100 patients, and the share of prescriptions for UTIs in the total number of antibiotics for systemic use. Years in service and completed specialization in family medicine did not significantly affect either the total number of prescriptions or the prescribing rates per 100 patients.

The percentage of prescriptions for UTIs in the total outpatient consumption varies, according to data from the literature, between 15% and 20%, but with large differences. Several studies of outpatient antimicrobial consumption based on electronic databases recorded 15% (20), 4.6% (21), and 22.7% (22) prescriptions related to UTIs. A study of antimicrobial consumption for genitourinary infections in women in five European countries (UK, Spain, Germany, the Netherlands, and Denmark) (23) recorded proportions between 8% – 16% (UK), 14% (Spain), 18% (Germany), 10% – 22% (Netherlands), and 19% (Denmark). In our study, 22% of prescriptions were issued for uncomplicated and complicated infections in both sexes, which roughly corresponds to the UK study of Dolk and al. (22), and 14.8% for uLUTIs in women over 18 years of age. Antimicrobial utilization showed large fluctuations between the lowest and highest prescribers, verified also by large interquartile ranges in both utilization segments.

To reduce the impact of the list size (varying almost three times), the consumption was expressed in rates per 100 patients. Additionally, the percentages of antibiotics for UTIs compared to all antibiotics for systemic use were analyzed, for each individual GP. The difference between the highest and lowest rates per 100 patients for all UTIs as well as for uLUTIs, as shown in Table 1, was about 6 times, while the proportion of prescriptions for UTIs compared to the total consumption varied slightly over 7 times. Some GPs showed excessively high percentages: team22 used almost half of all antibiotics (48.4%) for urinary infections, while its prescribing rate per 100 (8.08/100) was relatively inconspicuous (compared to the highest rate, 14.6/100). If assessed by only this criterion, we could say that he was an "economical prescriber". As opposed to team22, team10 had the lowest percentage (6.6%), or about 7 times less, while the list size was among the largest (2006 patients), and the second low-prescriber, team12 (9%) had 1335 patients in care. These figures, probably more than any other indicator, illustrate differences in attitudes and knowledge between individual GPs as potentially the most important factor explaining variations. It is difficult to explain six times variations (in rates per 100 patients) in uUTIs because these infections are characterized by recognizable clinical symptoms, absence of major comorbidities, and relatively simple diagnostics. Every GP and his patients form a complex system in the context of prescribing (24), which necessitates consideration of many variables in the analysis of each individual prescribing model.

We additionally compared prescribing in uLUTIs in women over 18 years with the ESAC quality indicators. Out of 3581 prescriptions for uLUTIs, 51% referred to first-line antibiotics, 17.9% to fluoroquinolones, and 30.3% to beta-lactams, which indicates sub-optimal compliance with both the quality indicators and national guidelines (12). Among the first-line antibiotics, there were 31% prescriptions for nitrofurantoin, 12.5% for fosfomycin, and 8% for co-trimoxazole. Relatively poor adherence to guidelines is found in several other studies. In a two-month study by Wellinga et al. the most prescribed drugs were co-amoxiclav (33.1%), followed by trimethoprim (26%), fluoroquinolones (17%), and nitrofurantoin (12%) (25), while a study from Spain reported fosfomycin (47.1%), fluoroquinolones - ciprofloxacin and norfloxacin (21.7%), co-amoxiclav (15.3%), and only 0.3% of nitrofurantoin (26). One of the main reasons for differences in the choice of antibiotics was, according to Llor and Bjerrum, professional attitudes and traditions regarding the treatment of infections in individual

countries (27). The proportion of beta-lactams (co-amoxiclav and cephalosporins) in our research was about 30%, similar to the result in a study investigating the appropriateness of treatment based on urine cultures (25). In both studies, GPs equally favored beta-lactams in an indication where they should actually be alternative drugs.

Quality indicators are a helpful tool in assessing the appropriateness of prescriptive practice and are generally in line with the recommendations of the guidelines (19). According to indicator "b" - the share of first-line antibiotics, our result was 51% (desirable range: 80%-100%), while indicator "c" (fluoroquinolones) was 17.9% (desirable range: 5%), thus significantly exceeding the recommended limit. Only one GP reached the level of first-line antibiotics above 80%, while the majority (25 teams or 59.5%) prescribed in the range of 50% – 80%, but still prescribing more than a half of the recommended antibiotics for uLUTIs. About a third of GPs (15 teams) prescribed mostly alternative antibiotics, thus clearly proving their erroneous attitudes that all the three antibiotic groups are much the same regarding efficacy and potential for collateral damage.

The relationship between specialization in family medicine and years in service with the number of prescriptions per 100 patients for uLUTIs was analyzed by Mann-Whitney U test. The lack of statistically significant correlation between the clinical experience and the prescriptions rate per 100 ($P = 0.51$) indicates that the experience per se is not among the most relevant factors shaping the prescriptive model. "Experienced GPs", with 15–30 years in service showed the prescribing pattern not much different from colleagues with less experience in family practice. But this conclusion is uncertain because data on the actual number of visits to each GP were not recorded, and thus the number of visits without antibiotics is unknown. The relationship between prescribing rates and specialization also did not reach statistical significance ($P = 0.51$). Lopez-Vasquez et al. have found a marginal impact of specialization on the extent of antibiotic prescribing (28). GPs with completed specialization did not significantly differ in the proportion of first-line antibiotics and fluoroquinolones compared to GPs without specialization.

Cutting down on antibiotic use in UTIs lead to a decrease in local levels of resistance (29). Given the growing trend of *E. coli* resistance in Croatia, prescribing nitrofurantoin (after considering contraindications) as the drug of choice for uLUTIs caused by both susceptible and resistant strains of *E. coli* is of key importance. Fluoroquinolone resistance in Enterobacteriaceae is on the rise globally, exceeding 50% in some parts of the world (30). About one to two-thirds of these strains produce extended-spectrum beta-lactamases, making them resistant to several important antibiotic subgroups: fluoroquinolones, beta-lactams, and co-trimoxazole. Nitrofurantoin has retained efficacy in uLUTIs caused by these bacteria and therefore represents the drug of choice for resistant infections in the future

Strengths and limitations

As our primary goal was to analyze the prescribing pattern in UTIs, diagnostic verification of symptoms (test strip and sediment, urine culture), identification of the causative pathogen, and antimicrobial susceptibility were not included in the follow-up. A too-small sample of doctors and the lack of data to confirm the diagnosis of urinary tract infection by objective methods (test strip, urine culture) are the main disadvantages. Due to the lack of data on bacterial pathogens, we could not determine the impact of resistant microorganisms on the number of prescriptions. The main advantage of our research is in the analysis of prescribing based on routine work in GPs' offices, as opposed to data from pharmacies or wholesalers.

Conclusion

The empirical therapy of urinary infections in a sample of GPs was suboptimal, both regarding indicators of the quality of prescribing and national guidelines. In reducing differences in prescribing practice, one of the important measures should be the feedback to physicians with excessively high prescribing rates, comparing their practice with "low-prescribers". GPs with low prescribing rates are proof that neither the number of patients on the list nor a number of other complex variables should negatively influence the prescribing model, once firm and correct attitudes about antimicrobial therapy are built.

Abbreviations

UTI – urinary tract infection, uUTI – uncomplicated urinary tract infection, GP – general practitioner, ESAC – European Surveillance of Antimicrobial Consumption, ATC – Anatomical Therapeutic Chemical classification system of drugs, HALMED – Croatian Agency for Medicinal Products, DDD TID – defined daily doses/1000 inhabitants/day.

Declarations

Ethics approval and consent to participate

Prior to commencing this research, the research plan was approved by the Ethics Committee of the Faculty of Medicine, Osijek, Croatia. The Ethics Committee assessed that the proposed research was multidisciplinary ethically acceptable and in accordance with the inaugurated basic ethical principles and human rights in biomedical research (class: 602-04 / 19-08 / 04, registration number: 2158-61-07-19-04, dated 25 January 2019). Informed consent was waived by the opinion of the Ethics Committee.

Consent for publication

Consents for publication was waived by the opinion of the Ethics Committee.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors declare that they have no competing interests.

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Author's contributions

ZV was involved in the conception of the study, data collection, analysis and interpretation, and original draft preparation. BP and NR participated in data collection. BP and NR were also involved in the critical revision of all versions of the manuscript. All authors have read and agreed to the published version of the manuscript

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