Infection (2019) 47:1027–1035
https://doi.org/10.1007/s15010-019-01361-y

ORIGINAL PAPER

Active surveillance of antibiotic resistance patterns in urinary tract infections in primary care in Switzerland

Andreas Plate[1] · Andreas Kronenberg[2] · Martin Risch[3] · Yolanda Mueller[4] · Stefania Di Gangi[1] · Thomas Rosemann[1] · Oliver Senn[1]

Received: 26 July 2019 / Accepted: 24 September 2019 / Published online: 8 October 2019

Abstract

Purpose Urinary tract infections (UTI) are one of the most common reasons for prescribing antibiotics in primary care. In Switzerland, the Swiss Center for Antibiotic Resistances (ANRESIS) provides resistance data by passive surveillance, which overestimates the true resistance rates. The aim of this study was to provide actual data of the antimicrobial resistance patterns in patients with UTI in Swiss primary care.

Methods From June 2017 to August 2018, we conducted a cross-sectional study in 163 practices in Switzerland. We determined the resistance patterns of uropathogens in patients with a diagnosis of a lower UTI and analyzed risk factors for resistance. Patients with age < 18 years, pregnancy or a pyelonephritis were excluded.

Results 1352 patients (mean age 53.8, 94.9% female) were included in the study. 1210 cases (89.5%) were classified as uncomplicated UTI. *Escherichia coli (E. coli)* was the most frequent pathogen (74.6%). Susceptibility proportions of *E. coli* to ciprofloxacin (88.9%) and trimethoprim-sulfamethoxazol (TMP/SMX) (85.7%) were significantly higher than the proportions reported by ANRESIS. We found high susceptibility to the recommended first-line antibiotics nitrofurantoin (99.5%) and fosfomycin (99.4%). Increasing age, antimicrobial exposure and a recent travel history were independently associated with resistance.

Discussion In this study, we report actual data on the resistance patterns of uropathogens in primary care in Switzerland. *Escherichia coli* showed low resistance rates to the recommended first-line antibiotics. Resistance to TMP/SMX was significantly lower than reported by ANRESIS, making TMP/SMX a suitable and cheap alternative for the empirical treatment.

Keywords Urinary tract infection · Resistance rates · Susceptibility rates · *E. coli* · Primary care · Switzerland

Introduction

Urinary tract infections (UTI) are one of the most common infections worldwide [1] and almost every second woman will have at least one episode during lifetime [2]. Although UTIs may be self-limiting, UTIs are one of the most common reasons for prescribing antibiotics in primary care [3]. A progress to an upper UTI/pyelonephritis is rare [4], but seems to be more common without antibiotic therapy. Furthermore, antibiotic therapy results in a faster symptom relief compared to placebo or anti-inflammatory therapies [5, 6]. Most guidelines do not recommend a microbiological diagnosis in cases of uncomplicated UTI (uUTI) before treatment [7, 8]. The choice of the empirical antibiotic treatment depends on the expected bacteria and their antibiotic resistance patterns. To date, fosfomycin, nitrofurantoin, pivmecillinam, and trimethoprim-sulfamethoxazol (TMP/

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s15010-019-01361-y) contains supplementary material, which is available to authorized users.

✉ Andreas Plate
andreas.plate@usz.ch

1 Institute of Primary Care, University and University Hospital of Zurich, Pestalozzistrasse 24, 8091 Zurich, Switzerland

2 Swiss Center for Antibiotic Resistance, Institute for Infectious Diseases, University Bern, Bern and Medix General Practice Network, Bern, Switzerland

3 Labormedizinisches zentrum Dr Risch Ostschweiz AG, Buchs, St. Gallen, Switzerland

4 Department of Family Medicine, Center for Primary Care and Public Health (Unisanté), University of Lausanne, Lausanne, Switzerland

SMX) were recommended as empirical first-line therapy in most guidelines. The use of TMP/SMX is limited to areas, where local resistance rates are known and where they do not exceed 20% [7]. In Switzerland, the Swiss Center for Antibiotic Resistances (http://www.anresis.ch) provides a nationwide passive surveillance [9]. However, because in cases of uUTI no microbiological diagnostic is done in most cases, passive surveillance may overestimate the resistance prevalence in the community setting [10]. The aim of this study was to provide actual data of the antimicrobial resistance patterns in patients with a lower UTI in primary care.

Methods

This cross-sectional study was conducted from June 2017 to August 2018 in 161 Swiss primary care practices as well as in two large "walk-in" practices. The general practitioners (GP) proposed study participation to all patients aged 18 and older with a clinical diagnosis of a lower UTI in consecutive order. Pregnant women and patients with a pyelonephritis were excluded. No patient could be included twice in the study in case of recurrence or treatment failure. Diagnostic criteria of an UTI (complicated and uncomplicated) were provided to all GPs to ensure diagnostic standardization [8]. UTI was defined as the new onset of typical symptoms (dysuria, pollakiuria, urgency or haematuria) and a positive urine dipstick (positive leucocytes). Uncomplicated cystitis was defined as cystitis in otherwise healthy women without the history or the clinical suspicion of any functional or anatomical abnormalities of the urinary tract. UTIs in male or in female patients with concomitant (urological) disorders (according to Swiss national guidelines [8]) were considered as complicated. In case of study participation and signed informed consent, a urine specimen was collected for microbiological analysis. Furthermore, epidemiological and clinical data were recorded. Finally, the GP had to determine the final diagnosis (uncomplicated or complicated cystitis) and if he/she would have done a microbiological analysis apart of the study situation.

Resistance data from ANRESIS (2018 resistance data) were acquired using the following selection criteria: All urinary *Escherichia coli* (*E. coli*) isolates from adult (age > 15) outpatients (private physicians, ambulatories or emergency departments), (Assessed 17 June 2019) (http://www.anresis.ch). Comparisons of regional susceptibility patterns were done according to the geographical classification of Switzerland done by ANRESIS.

Microbiological analysis

Urine samples for culture were collected in a sterile container containing boric acid as a preservative. The urine was plated onto a chromogenic and blood agar medium and an inhibition test for detection of a possible antibiotic pretreatment was performed. After 24/48 h incubation time, positive culture was defined as growth of 10^3 colony-forming units or more. Bacteria were subjected to an identification procedure by mass spectrometry (MALDI TOF) and to an automated antimicrobial susceptibility testing (Vitek 2). Intermediate resistance was handled as resistant for resistance analysis.

Ethics

The study was approved by the local ethics committee (BASEC Number: 2016-01918) and every patient signed a study-specific informed consent.

Analysis

Summary statistics were reported as means (standard deviation, SD), and number (percentage, %) as appropriate. Patient characteristics and microbiological results were compared between cUTI and uUTI; Independent sample Student's t test was used for continuous variables and Chi square or Fisher's test, as appropriate, was used for categorical variables. Antibiotic susceptible rates of *E. coli* were compared to the rates provided by Swiss passive surveillance using the Chi squared test with simulated *p*-values, computed by a Monte Carlo test with 2000 replicates. The 95% confidence interval (CI) for the susceptible proportions was reported, too. Resistance to Fluoroquinolones (FC) means resistance to at least one out of ciprofloxacin, levofloxacin, moxifloxacin, or norfloxacin. Univariable and multivariable logistic regression models were performed to identify the association between patient characteristics, together with type of UTI, and antibiotics resistance rate of *E. coli*. Only women infected with *E. coli* were considered in the regression analysis. The study's exploratory nature required non-parsimonious multivariable regression models to identify variables for further exploration in future studies. These models were performed using automatic stepwise selection estimation with likelihood ratio testing (P value ≤ 0.20) specified as the test of significance to include or exclude variables. For all other tests, $P \leq 0.05$ was considered statistically significant. As sensitivity analysis, we estimated the intracluster correlation coefficient (ICC), using a mixed regression model with a random effect at GP level. All analyses were carried out using statistical package R, R Core Team (2016). (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Results

1454 patients were screened for study participation. 33 patients refused to participate. In total, 1421 urine samples were collected (Fig. 1). 69 patients were excluded due to missing leukocyturia (46), age < 18 (10), absence of classical symptoms (9), pregnancy (2), or other reasons (2). Finally, 1352 urine samples were included in the overall analysis. Basic demographic and clinical information are shown in Table 1. 1210 cases (89.5%) were reported as uUTI and 129 as cUTI (9.5%). Thirteen cases (1%) resulted unclassified; hence these cases were excluded for comparison analysis, but still included in the overall analysis. 94.9% of the participants were females. The overall mean age was 53.75 (standard deviation: 20.8) years.

Microbiological analysis

Urine cultures were positive in 87.1% (1117 cases) (Table 2). In 143 cases (12.1%) two pathogens were detected and 140 cases (11.9%) were considered as contaminated due to growth of three or more pathogens and were excluded from further analysis. Gram-negative rods were present in 86.8%, enterococci in 6.9%, and other gram-positive bacteria in 19.4% of all cases. However, growth of only gram-negative rods, enterococci or other gram-positive bacteria in a culture was detected in 72.7%, 3.2%, and 8.6%, respectively. *Escherichia coli* was the most common pathogen and was found in 74.6% of all cases. Comparing the causing uropathogens in the uUTI and cUTI, there were no significant differences.

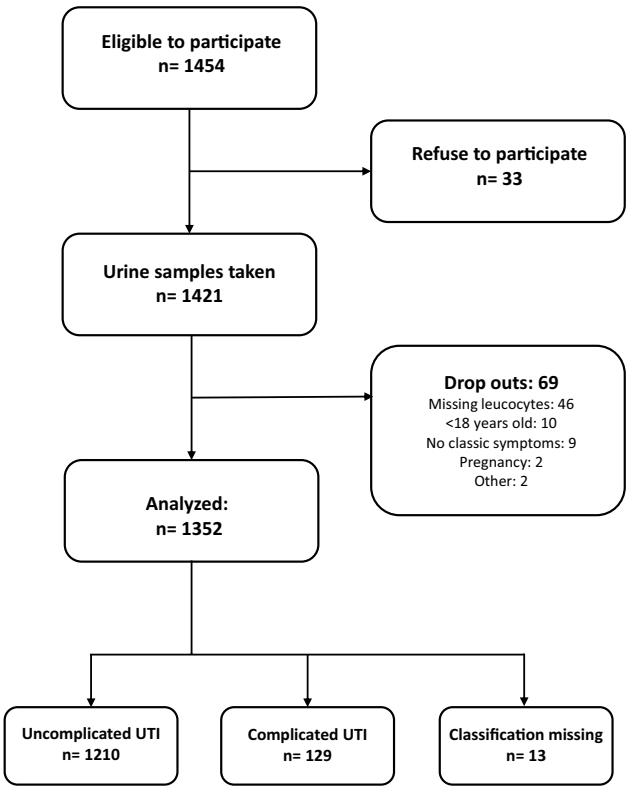

Fig. 1 Flowchart of 1454 eligible patients with the diagnosis of a urinary tract infection

Resistance proportions

Resistance proportions were reported for *E. coli* (additional resistance proportions for *Klebsiella* spp., *Enterobacter* spp. and *Proteus* spp. were provided in Supplemental Table 4). *Escherichia coli* showed high susceptibility rates to the recommended first-line antibiotics fosfomycin [99.35%, 95% confidence interval (CI): 99.34–99.37%], nitrofurantoin (99.48%, 95% CI: 99.47–99.5%), and TMP/SMX (85.66%, 95% CI: 85.58–85.74%). With exception of the Geneva area, resistance proportions to TMP/SMX were below 20% in all areas of Switzerland. Although not statistically significant, we observed the lowest susceptibility proportions against TMP/SMX in the French-speaking western areas of Switzerland. 88.89% (95% CI 88.82–88.96%) of the isolates were susceptible to ciprofloxacin (Table 3) and 85.40% (95% CI: 85.32–85.48%) of the isolates were susceptible to norfloxacin. In comparison to the data provided by ANRESIS (passive surveillance), we found significantly higher susceptibility proportions of *E. coli* to both TMP/SMX and ciprofloxacin ($p < 0.001$ in both groups). There were no significant differences in the susceptibility to fosfomycin and nitrofurantoin ($p = 0.14$, and $p = 0.543$, respectively) between active and passive surveillance. With the exception of nitrofurantoin ($p = 0.011$), susceptible proportions to the antibiotics did not differ significantly between the different regions across Switzerland in our study. Nitrofurantoin susceptibility was reduced in the south region of Switzerland (susceptibility rate 90.9%), compared to the other regions (susceptibility rates > 97.3%). However, this finding could be biased due to the very limited specimen numbers in the south region ($n = 11$).

Comparing the susceptibility proportions of *E. coli* in uUTI and cUTI, we found no significant differences (Supplemental Table 1). Furthermore, there was no significant difference in the susceptibility proportion to TMP/SMX in patients in which the GP would have done a urine analysis apart from the study, compared to the patients without a urine analysis. In contrast, susceptibility to ciprofloxacin was significant lower in patients in which the GP would have done a urine analysis apart from the study (Supplemental Table 2).

Table 1 Basic characteristics of 1352 analyzed patients with uncomplicated or complicated urinary tract infection

	Total *N* = 1352	uUTI *N* = *1210*	cUTI *N* = *129*
Demographic data			
Gender *N* (%)			
F	1283 (94.9)	1210 (100.0)	60 (46.5)
M	69 (5.1)	0 (0.0)	69 (53.5)
Age (mean, sd)	53.75 (20.83)	53.16 (20.88)	58.75 (19.90)
Living situation			
Living at home	1331 (99.1)	1192 (99.3)	127 (98.4)
Long-term care	12 (0.9)	9 (0.7)	2 (1.6)
Hospital stay within the past 6 months (yes)	136 (10.1)	116 (9.6)	20 (15.9)
Antimicrobial exposure during the past 3 months	348 (26.0)	297 (24.8)	45 (36.0)
Intake of phytotherapeutics for prevention of UTI			
Overall:	375 (28.1)	340 (28.5)	31 (24.6)
Cranberries	180 (13.5)	162 (13.6)	17 (13.5)
Mannose	104 (7.8)	95 (8.0)	7 (5.6)
Other	178 (13.4)	161 (13.5)	16 (12.7)
Prior catheterization			
Within the past 4 weeks	19 (1.4)	13 (1.1)	5 (3.9)
Within the past 3 months	15 (1.1)	8 (0.7)	7 (5.4)
History of UTI	1106 (82.4)	1007 (83.8)	87 (68.0)
Reason for GP consultation: Suspected UTI	1237 (92.2)	1112 (92.5)	115 (90.6)
Clinical data			
Symptoms			
Dysuria	1075 (79.5)	968 (80.0)	99 (76.7)
Pollakisuria	968 (71.6)	880 (72.7)	84 (65.1)
Urgency	997 (73.7)	896 (74.0)	92 (71.3)
Hematuria	272 (20.1)	245 (20.2)	26 (20.2)
Other	312 (23.1)	274 (22.6)	33 (25.6)
Laboratory results			
Pathologic urine dipstick test			
Leukocytes positive	1352 (100)	1210 (100)	129 (100)
Erythrocytes positive	394 (30.5)	331 (28.7)	58 (45.7)
Nitrite positive	1119 (84.3)	1000 (84.1)	108 (85.7)
Culture would have been done during usual care (yes)	563 (41.7)	446 (37.0)	109 (84.5)

Data shown as absolute numbers and in percentage (in parenthesis). Due to missing values (range: $n = 9$ to $n = 60$) proportions do not round up to 100%

uUTI uncomplicated urinary tract infection, *cUTI* complicated urinary tract infection, *F* female, *M* male, *sd* standard deviation, *GP* general practitioner

Risk factors for *E. coli* resistance

Univariate and multivariate logistic regression analysis for identifying variables as risk factors for antibiotic resistance to the recommended first-line antibiotics (TMP/SMX, nitrofurantoin, and fosfomycin) or to FC in women infected with *E. coli* are shown in Table 4. Additional analysis for each antibiotic in separate are provided in Supplemental Table 3. Clustering by GP practice was negligible, with ICC 0.012 for resistance to first-line antibiotics.

Analysing risk factors for resistance to any recommended first-line antimicrobial agent, antibiotic exposure for any reason within the past 3 months and a recent travel to Africa were associated with an increased risk of resistance, which is also true for resistance to TMP/SMX alone. Compared to antimicrobial exposure for any reason, antimicrobial exposure specific for an UTI was not associated with an increased resistance. Age, a recent hospital stay, and a travel history to Oceania were associated with increased risk of resistance to fosfomycin, whereas no risk factors could be identified for resistance to nitrofurantoin. Resistance to FC was associated with age, living in long-term care, antimicrobial exposure, and traveling within Europe and Asia.

Table 2 Microbiological results of 1352 urine samples

	Total $N=1352$	uUTI $n=1210$	cUTI $n=129$	Statistics (where applicable)
Positive culture	1177 (87.1)	1055 (87.2)	112 (86.8)	1.000
One pathogen	894 (76.0)	803 (76.1)	85 (75.9)	0.655
Two pathogens	143 (12.1)	126 (11.9)	16 (14.3)	–
Contamination[+]	140 (11.9)	126 (11.9)	11 (9.8)	–
Positive culture with only*				
Gram-negative rods	754 (72.7)	676 (72.8)	72 (71.3)	0.842
Gram-positive bacteria (excl. Enterococci)	89 (8.6)	83 (8.9)	6 (5.9)	0.406
Enterococci	33 (3.2)	27 (2.9)	6 (5.9)	0.178
Presence of gram-negative rods	900 (86.8)	806 (86.8)	87 (86.1)	0.984
Acinetobacter ursingii	1 (0.1)	0 (0.0)	0 (0.0)	–
Citrobacter spp	19 (1.8)	15 (1.6)	4 (4.0)	0.202
Enterobacter spp	12 (1.2)	11 (1.2)	1 (1.0)	–
Escherichia coli	774 (74.6)	695 (74.8)	73 (72.3)	0.664
Klebsiella spp	62 (6.0)	56 (6.0)	6 (5.9)	1.000
Proteus spp	42 (4.0)	39 (4.2)	3 (3.0)	0.743
Pseudomonas aeruginosa	2 (0.2)	1 (0.1)	1 (1.0)	0.470
Ralstonia spp	1 (0.1)	0 (0.0)	1 (1.0)	–
Raoultella ornithinolytica	1 (0.1)	1 (0.1)	0 (0.0)	–
Morganella morganii	2 (0.2)	1 (0.1)	1 (1.0)	0.470
Presence of gram-positive bacteria	272 (26.2)	245 (26.4)	26 (25.7)	0.986
Aerococcus spp.	10 (1.0)	9 (1.0)	1 (1.0)	1.000
Streptococci	89 (5.7)	81 (8.7)	8 (7.9)	0.932
Gardnerella vaginalis	16 (1.5)	16 (1.7)	0	–
Lactobacillus spp.	36 (3.5)	34 (3.7)	2 (2.0)	0.557
Staphylococcus aureus	13 (1.3)	10 (1.2)	3 (3.0)	0.308
SCN	38 (3.7)	37 (4.0)	1 (1.0)	0.216
Enterococcus faecalis	72 (6.9)	59 (6.4)	12 (11.9)	0.061

Data shown as absolute numbers and in percentage (in parenthesis)

SCN Staphylococci coagulase negative, *uUTI* uncomplicated urinary tract infection, *cUTI* complicated urinary tract infection

[+]Growth of three or more pathogens were considered as contamination

*Excluding contaminated samples

Discussion

In this study, we determined the frequency and susceptibility proportions of uropathogens in urinary tract infections in primary care in Switzerland. We found high susceptibility proportions of *E. coli* to the recommended first-line antibiotics and higher susceptibility proportions for TMP/SMX and ciprofloxacin as reported by the Swiss national passive surveillance.

Escherichia coli is the most frequent pathogen in both uncomplicated and complicated UTI [11] and accounts for up to 95% of urinary tract infections [7] as also seen in our study. Knowledge of local resistance patterns of *E. coli* is, therefore, crucial for the consideration of an adequate empirical treatment. In our cohort, clinical significant growth, after excluding contaminated samples, could be detected in 76%, which is similar to other studies [10, 12]. *Escherichia coli* was the most frequent pathogen and showed high susceptibility proportions to the recommended first-line antibiotics fosfomycin, nitrofurantoin, and TMP/SMX. Current guidelines recommend the use of TMP/SMX only if local susceptibility proportions exceed 80%. With exception of the Geneva area, this premise is fulfilled in all geographic areas of Switzerland. Although not statistically significant, we observed a trend for higher resistance proportions against TMP/SMX in the French-speaking western areas of Switzerland. This could be explained by the fact that the highest antibiotic prescription rates are also seen the French-speaking parts of Switzerland [13, 14] and an association between resistance

Table 3 Susceptibility rates of *E. coli* in our cohort compared to data provided by Swiss passive surveillance

	Fosfomycin			Nitrofurantoin			TMP/SMX			Ciprofloxacin		
	Study $p=0.443^{+}$	Anresis	*P*	Study $p=0.011^{+}$	Anresis	*P*	Study $p=0.873^{+}$	Anresis	*P*	Study $p=0.555^{+}$	Anresis	*P*
Central-East $N=89$	97.8	98.4 $N=1161$	0.638	100	99.5 $N=1160$	1.000	83.1	80.6 $N=1162$	0.574	89.9	84.9 $N=1162$	0.220
Central-West $N=151$	99.3	98.8 N=10,018	0.740	99.3	98.8 $N=10,641$	0.733	87.4	76.9 $N=10,641$	**0.002**	88.1	83.4 $N=9649$	0.147
East $N=124$	99.2	98.9 $N=1943$	1.000	100	99.3 $N=1944$	0.627	84.7	76.9 $N=1947$	**0.049**	93.5	82.4 $N=1948$	**0.003**
Geneva area $N=17$	100	98.3 $N=4152$	1.000	100	99.3 $N=4154$	1.000	76.5	76.7 $N=4162$	1.000	88.2	81.1 $N=4162$	0.569
Nord-East $N=143$	100	99.1 $N=4070$	0.393	100	99.6 $N=4068$	0.671	86.0	79.9 $N=4080$	0.084	84.6	85.9 $N=4080$	0.713
North-West $N=158$	100	98.7 $N=6948$	0.177	100	99.4 $N=6949$	0.646	87.3	76.9 $N=6968$	**0.002**	88.0	83.2 $N=6978$	0.114
South $N=11$	100	98.7 $N=1778$	1.000	90.9	99.7 $N=1779$	**0.038**	90.9	78.8 $N=1783$	0.465	90.9	81.9 $N=1782$	0.700
West $N=75$	98.7	98.9 $N=5574$	1.000	97.3	99.3 $N=5591$	0.111	82.7	77.4 $N=5600$	0.332	90.7	83.2 $N=5568$	0.133
Total: $N=774$	99.4	98.8 $N=35,644$	0.140	99.5	99.2 $N=36,286$	0.543	85.7	77.5 $N=36,343$	**<0.001**	88.9	83.3 $N=35,329$	**<0.001**

Regional data were available in 768 (99.2%) cases. Data shown in percentages. Study: susceptibility rates in our cohort. Anresis: susceptibility rates (2018) provided by the Swiss national resistance center

^{+}p value refers to overall comparison across regions

Table 4 Logistic regression analysis for *E. coli* resistance

Variable	Resistance to recommended first-line antibiotics fosfomycin, TMP/SMX, and nitrofurantoin				Resistance to chinolone antibiotics*			
	Univariable analysis		Multivariable analysis $N=716$		Univariable analysis		Multivariable analysis $N=710$	
	OR (95% CI)	*P*-value	OR (CI 95%)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age ($N=735$)	1.01 (0.99, 1.02)	0.105	**1.01 (1.00, 1.02)**	**0.042**	**1.01 (1, 1.02)**	**0.024**	**1.02 (1.01, 1.03)**	**0.005**
cUTI (ref. uncomplicated), ($N=729$)	0.90 (0.30, 2.18)	0.827			1.79 (0.74, 3.9)	0.164		
Living situation: long-term care (ref. living at home) ($N=729$)	1.03 (0.05, 6.43)	0.982			**5.63 (1.03, 30.8)**	**0.036**	**5.23 (0.92, 29.62)**	**0.050**
Hospital stay within the past 6 months, ($N=729$)	1.25 (0.65, 2.26)	0.479			1.36 (0.70, 2.46)	0.333		
Antimicrobial exposure during the past 3 months, ($N=728$)	**1.87 (1.20, 2.87)**	**0.005**	**1.84 (1.17, 2.87)**	**0.007**	**1.85 (1.18, 2.87)**	**0.006**	**2.87 (1.40, 5.63)**	**0.003**
Antimicrobial exposure during the past 3 months for UTI, ($N=728$)	1.42 (0.84, 2.32)	0.179			1.33 (0.77, 2.21)	0.284	0.51 (0.23, 1.16)	0.102
Intake of phytotherapeutics for prevention of UTI, ($N=725$)	0.84 (0.53, 1.29)	0.434			0.878 (0.55, 1.37)	0.575		
Prior catheterization, ($N=718$)	0.95 (0.15, 3.61)	0.950			1.68 (0.37, 5.59)	0.438		
History of UTI, ($N=731$)	0.88 (0.54, 1.5)	0.628			1.17 (0.68, 2.1)	0.585		
Traveling outside CH in the past 12 months, ($N=723$)	1.10 (0.73, 1.66)	0.661			1.18 (0.78, 1.82)	0.428		
Traveling to Europe, ($N=723$)	0.98 (0.66, 1.46)	0.916			1.17 (0.78, 1.75)	0.460	**1.55 (1.00, 2.43)**	**0.050**
Traveling to Asia, ($N=723$)	1.22 (0.57, 2.42)	0.582			1.90 (0.95, 3.59)	0.058	**2.52 (1.22, 4.96)**	**0.009**
Traveling to Africa, ($N=723$)	**2.54 (1.01, 5.87)**	**0.034**	**3.16 (1.24, 7.45)**	**0.011**	1.40 (0.46, 3.53)	0.514	2.02 (0.64, 5.33)	0.183
Traveling to North America, ($N=723$)	1.77 (0.68, 4.08)	0.202	2.15 (0.80, 5.20)	0.102	1.21 (0.40, 3.01)	0.708		
Traveling to South America, ($N=723$)	1.91 (0.52, 5.71)	0.273	2.48 (0.66, 7.66)	0.137	1.39 (0.31, 4.46)	0.615		
Traveling to Oceania, ($N=723$)	3.50 (0.46, 21.32)	0.173			3.72 (0.49, 22.73)	0.152	3.98 (0.48, 26.60)	0.154

Only females infected by *E. coli* ($N=735$) were included. In multivariable analysis predictors with $p<0.2$ were included. Unless otherwise stated, reference category (ref) for each categorical variables is "no". Significant results are written in bold

cUTI complicated Urinary tract infection, *CH* Switzerland, *CI* confidence interval, *OR* odds-ratio, *n* number of patients

*Resistance to Chinolone antibiotics means resistance to at least one out of ciprofloxacin, levofloxacin, moxifloxacin, or norfloxacin

rates and antibiotic prescription is frequently reported in the literature [14, 15].

Compared to the Swiss national passive surveillance, susceptibility proportions to TMP/SMX and ciprofloxacin were significantly higher in our cohort. This reflects the selection bias in passive surveillance systems, as microbiological analysis is not recommended in most outpatients with a uUTI and higher resistance rates are seen in patients with a cUTI [16]. Susceptibility proportions of nitrofurantoin and fosfomycin did not differ significantly from the reported proportions by ANRESIS. This is due to overall high susceptibility proportions (> 98%) in both our cohort and ANRESIS.

10 years ago, a similar study investigated the resistance proportions in around 1000 outpatient UTI cases in the canton of Berne in Switzerland [10]. The reported susceptibility proportions of *E. coli* to TMP/SMX (71–80%) were lower than the susceptibility proportions in our study. The same is true for nitrofurantoin, with higher susceptibility

proportions in our study. Resistance proportions to fosfomycin were similar in both studies. It seems that at least in the outpatient setting there is no deterioration of resistance patterns against fist-line antimicrobial agents within the past decade, which is remarkable as the frequency of resistant uropathogens is steadily increasing [16, 17]. On the other hand, susceptibility to norfloxacin (the only reported FC), was reported higher compared to our study.

It is generally considered that susceptibility rates of uropathogens in uUTI are higher compared to cUTI [7, 12, 18–21] and that *E. coli* is the most common uropathogen in both conditions, despite the wider microbiological spectrum in cUTI [22]. As expected in our study, *E. coli* was the most frequent pathogen in both uUTI and cUTI (74.8% and 72.3%, respectively), but susceptibility proportions did not differ significantly between both groups. These findings could be explained by two reasons: First, the numbers of cUTI were relatively low (< 10%). Second, in contrast to the well-known and accepted definition of uUTI, the definition for cUTI is more heterogeneous. There is evidence that, for example, in young men a UTI can be uncomplicated [23]. The microbiological patterns of causing pathogens in the different aetiologies of cUTI are unknown. Our findings, that there can be similarities in the resistance patterns and in the causing pathogens in both groups, support the need for a more detailed stratification and treatment recommendations of cUTI [11, 23] (at least for ambulatory care). National guidelines recommend a microbiological culture and the use of antibiotics with a good prostate penetration in UTI in men [8]. Both TMP/SMX and FC have an excellent prostate penetration. Due to the similar resistance rates in uUTI and cUTI in our cohort, empirical therapy with TMP/SMX seems to be feasible also in men until resistance analysis is available. According to pharmacological data also fosfomycin has a good penetration into the prostate [24], but today fosfomycin is not routinely used in the treatment of an prostatitis [22]. In contrast, nitrofurantoin does not penetrate into prostatic tissue adequately [25].

Multivariable regression analysis revealed age, prior antibiotic exposure, and a recent travel history as risk factors for antibiotic resistance. These findings are consistent with the known risk factors reported in the literature [26–29] and these factors need to be considered in the choice of the empiric treatment.

Strengths/limitations: In this prospective trial, we sampled urine specimen across all regions in Switzerland and all specimen were analyzed in one central laboratory. The overall numbers of patients that refused to participate and the exclusions were low (Fig. 1), indicating a low risk of selection bias, assuming the data are representative of primary care in Switzerland; nevertheless, certain subgroup analyses have to be interpreted with caution due to small sample sizes (e.g. comparisons across regions, multivariable modeling) and limited data (reason for classification uUTI vs. cUTI).

Implications for Swiss primary care

Current national and international guidelines recommend fosfomycin or nitrofurantoin for the empirical treatment of uUTI. Depending on the local resistance rate, TMP/SMX is an additional first-line antimicrobial agent. In our cohort, we could report resistance proportions below 20% to TMP/SMX in nearly all areas of Switzerland. Thus, TMP/SMX remains a suitable antibiotic for the empirical treatment of uUTI and even cUTI in primary care in Switzerland, especially as the treatment costs of the standard regime TMP/SMX are similar to that of nitrofurantoin, but three times cheaper compared to fosfomycin. However, in patients with a systemic antibiotic exposure within the past 3 months or a travel history to Africa, clinicians should prefer a therapy with nitrofurantoin or fosfomycin, Of note, a recent multicentric study showed superiority of nitrofurantoin over fosfomycin [30].

In our cohort *E. coli* isolates showed high susceptibility proportions to FC. FC are highly effective in the treatment of UTIs and were recommended for the empirical therapy for many years. Despite UTIs, FC are important in the treatment in extra-urogenital infections like intra-abdominal infections, soft tissue, and bone and joint infections. Due to excessive use, increasing resistance rates not only in uropathogens were observed [7]. Increasing FC resistance rates are a serious public health treat [16], in addition to the general potential side effects like ecological damage to gut flora or tendinopathies. Therefore, we support the recommendations of current guidelines to avoid FC use in the empirical therapy in UTI [7, 8] despite the low resistance proportions.

In conclusion, we could show low resistance patterns to the recommended first-line antibiotics fosfomycin, nitrofurantoin, and TMP/SMX in both uncomplicated and complicated UTI in primary care in Switzerland.

Acknowledgements We wish to thank primary care physicians and patients that participated in the study; we acknowledge Swiss family medicine institutes in Geneva, Lausanne, Lucerne, Basel and Zürich, the representatives of the local medical networks that supported recruitment of family physicians and the anresis-laboratories for sharing their data; we acknowledge Dr. phil. II Michael Ritzler und Dr. scient. med. Nadia Wohlwend as well as all involved laboratory members of the laboratory Risch, which performed all urine analysis for this study.

Funding This study was supported by grants from SwissLife, Blumenau-Léonie Hartmann Foundation, and Innova Foundation. ANRESIS is funded by the Swiss federal office of public health and the University of Bern. They had no influence over the study design, study results, interpretation of the data and publication.

Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

References

1. Foxman B. The epidemiology of urinary tract infection. Nat Rev Urol. 2010;7:653–60. https://doi.org/10.1038/nrurol.2010.190.
2. Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. Am J Med. 2002;113:5s–13s.
3. Petersen I, Hayward AC. Antibacterial prescribing in primary care. J Antimicrobi Chemother. 2007;60:i43–7. https://doi.org/10.1093/jac/dkm156.
4. Ikaheimo R, Siitonen A, Heiskanen T, Karkkainen U, Kuosmanen P, Lipponen P, et al. Recurrence of urinary tract infection in a primary care setting: analysis of a 1-year follow-up of 179 women. Clin Infect Dis. 1996;22:91–9.
5. Falagas ME, Kotsantis IK, Vouloumanou EK, Rafailidis PI. Antibiotics versus placebo in the treatment of women with uncomplicated cystitis: a meta-analysis of randomized controlled trials. J Infect. 2009;58:91–102. https://doi.org/10.1016/j.jinf.2008.12.009.
6. Kronenberg A, Butikofer L, Odutayo A, Muhlemann K, da Costa BR, Battaglia M, et al. Symptomatic treatment of uncomplicated lower urinary tract infections in the ambulatory setting: randomised, double blind trial. BMJ (Clin Res ed). 2017;359:j4784. https://doi.org/10.1136/bmj.j4784.
7. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for microbiology and infectious diseases. Clin Infect Dis. 2011;52:e103–20. https://doi.org/10.1093/cid/ciq257.
8. Hasse B, Egger M, Zanetti G, Marschall J, Mühlemann K, Harbarth S. Behandlung von unkomplizierten Harnwegsinfektionen. 2014.
9. Swiss Centre for Antibiotic resistance. 2018. http://www.anresis.ch. Accessed 23 Sept 2018.
10. Kronenberg A, Koenig S, Droz S, Muhlemann K. Active surveillance of antibiotic resistance prevalence in urinary tract and skin infections in the outpatient setting. Clin Microbiol Infect. 2011;17:1845–51. https://doi.org/10.1111/j.1469-0691.2011.03519.x.
11. Hooton TM. Clinical practice. Uncomplicated urinary tract infection. N Engl J Med. 2012;366:1028–37. https://doi.org/10.1056/nejmcp1104429.
12. Klingeberg A, Noll I, Willrich N, Feig M, Emrich D, Zill E, et al. Antibiotic-resistant *E. coli* in uncomplicated community-acquired urinary tract infection. Deutsches Arzteblatt Int. 2018;115:494–500. https://doi.org/10.3238/arztebl.2018.0494.
13. Filippini M, Masiero G, Moschetti K. Socioeconomic determinants of regional differences in outpatient antibiotic consumption: evidence from Switzerland. Health policy (Amsterdam, Netherlands). 2006;78:77–92. https://doi.org/10.1016/j.healthpol.2005.09.009.
14. Achermann R, Suter K, Kronenberg A, Gyger P, Muhlemann K, Zimmerli W, et al. Antibiotic use in adult outpatients in Switzerland in relation to regions, seasonality and point of care tests. Clin Microbiol Infect. 2011;17:855–61. https://doi.org/10.1111/j.1469-0691.2010.03348.x.
15. Pluss-Suard C, Pannatier A, Kronenberg A, Muhlemann K, Zanetti G. Hospital antibiotic consumption in Switzerland: comparison of a multicultural country with Europe. J Hosp Infect. 2011;79:166–71. https://doi.org/10.1016/j.jhin.2011.05.028.
16. Hooton TM, Besser R, Foxman B, Fritsche TR, Nicolle LE. Acute uncomplicated cystitis in an era of increasing antibiotic resistance: a proposed approach to empirical therapy. Clin Infect Dis. 2004;39:75–80. https://doi.org/10.1086/422145.
17. ECDC. Surveillance of antimicrobial resistance in Europe 2017. Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net) 2017.
18. Wagenlehner FM, Naber KG. Current challenges in the treatment of complicated urinary tract infections and prostatitis. Clin Microbiol Infect. 2006;12:67–80. https://doi.org/10.1111/j.1469-0691.2006.01398.x.
19. Peterson J, Kaul S, Khashab M, Fisher A, Kahn JB. Identification and pretherapy susceptibility of pathogens in patients with complicated urinary tract infection or acute pyelonephritis enrolled in a clinical study in the United States from November 2004 through April 2006. Clin Ther. 2007;29:2215–21. https://doi.org/10.1016/j.clinthera.2007.10.008.
20. Hitzenbichler F, Simon M, Holzmann T, Iberer M, Zimmermann M, Salzberger B, et al. Antibiotic resistance in *E. coli* isolates from patients with urinary tract infections presenting to the emergency department. Infection. 2018;46:325–31. https://doi.org/10.1007/s15010-018-1117-5.
21. Almomani BA, Hayajneh WA, Ayoub AM, Ababneh MA, Al Momani MA. Clinical patterns, epidemiology and risk factors of community-acquired urinary tract infection caused by extended-spectrum beta-lactamase producers: a prospective hospital case–control study. Infection. 2018;46:495–501. https://doi.org/10.1007/s15010-018-1148-y.
22. Bonkat G, Bruyère F, Cai T, Geerlings SE, Köves B, Schubert S, Wagenlehner F. Urological infections guidelines 2018.
23. Johansen TE, Botto H, Cek M, Grabe M, Tenke P, Wagenlehner FM, et al. Critical review of current definitions of urinary tract infections and proposal of an EAU/ESIU classification system. Int J Antimicrob Agents. 2011;38:64–70. https://doi.org/10.1016/j.ijantimicag.2011.09.009.
24. Zhanel GG, Zhanel MA, Karlowsky JA. Oral fosfomycin for the treatment of acute and chronic bacterial prostatitis caused by multidrug-resistant *Escherichia coli*. Can J Infect Dis Med Microbiol. 2018;2018:1404813. https://doi.org/10.1155/2018/1404813.
25. Lipsky BA, Byren I, Hoey CT. Treatment of bacterial prostatitis. Clin Infect Dis. 2010;50:1641–52. https://doi.org/10.1086/652861.
26. Tenney J, Hudson N, Alnifaidy H, Li JTC, Fung KH. Risk factors for acquiring multidrug-resistant organisms in urinary tract infections: a systematic literature review. Saudi Pharm J. 2018;26:678–84. https://doi.org/10.1016/j.jsps.2018.02.023.
27. Garau J, Xercavins M, Rodriguez-Carballeira M, Gomez-Vera JR, Coll I, Vidal D, et al. Emergence and dissemination of quinolone-resistant *Escherichia coli* in the community. Antimicrob Agents Chemother. 1999;43:2736–41.
28. Alós JI, Serrano MG, Gómez-Garcés JL, Perianes J. Antibiotic resistance of *Escherichia coli* from community-acquired urinary tract infections in relation to demographic and clinical data. Clin Microbiol Infect. 2005;11:199–203. https://doi.org/10.1111/j.1469-0691.2004.01057.x.
29. Ukah UV, Glass M, Avery B, Daignault D, Mulvey MR, Reid-Smith RJ, et al. Risk factors for acquisition of multidrug-resistant *Escherichia coli* and development of community-acquired urinary tract infections. Epidemiol Infect. 2018;146:46–57. https://doi.org/10.1017/S0950268817002680.
30. Huttner A, Kowalczyk A, Turjeman A, Babich T, Brossier C, Eliakim-Raz N, et al. Effect of 5-day nitrofurantoin vs single-dose fosfomycin on clinical resolution of uncomplicated lower urinary tract infection in women: a randomized clinical trial. Effect of nitrofurantoin vs fosfomycin on uncomplicated lower UTI in women. Effect of nitrofurantoin vs fosfomycin on uncomplicated lower UTI in women. JAMA. 2018;319:1781–9. https://doi.org/10.1001/jama.2018.3627.