ORIGINAL ARTICLE

Antibiotic prescription rate for upper respiratory tract infections in general practice – a Croatian study

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ABSTRACT

Aim Acute upper respiratory tract infections are the most common indication for antibiotic prescribing in primary care. The frequency of antibiotics prescribed to patients with upper respiratory tract infections has been studied.

Methods A cross-sectional survey has been conducted from October to December 2017 with participation of 17 General Practices in Croatia. Visits of patients with symptoms of upper respiratory tract infections made the survey framework. A specially structured questionnaire was a tool for the assessment of reasons for encounters, clinical statuses and practitioners' decisions. According to the registered clinical status, two independent doctors classified patients using Centor criteria, which were used to evaluate appropriate indication for antibiotic prescription.

Results The survey analysed 709 patients' visits. Seventy three percent of general practice visits due to acute respiratory tract infection were initial. Antibiotics had been prescribed in the total of 32.6% of cases. Analysing upper respiratory tract infections with Centor score 1 and 2, antibiotics had been prescribed in 22.8% cases of the first visit and in 31.7% of the second visit, and with the Centor score 3 and 4 antibiotics had been prescribed in 85.1% of cases during the initial visit, and 66.7% of cases during the second visit. Logistic regression analysis about the contribution of nonclinical variables to antibiotic prescribing showed that most often antibiotics had been prescribed on Mondays. The most prescribed group of antibiotics was the penicillin group (74.8%), followed by macrolides (17.6%) and cephalosporins (4.0%).

Conclusion General practitioners prescribe antibiotics for acute respiratory tract infections more than recommended by evidence based medicine and professional criteria.

Key words: antibiotic prescribing, Centor criteria, primary care

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INTRODUCTION

The increasing antibiotic resistance is a growing public health concern. According to literature more than 90% of prescriptions for antibiotics are issued in primary healthcare (1,2), and the majority for preschool children (3). The most common indication for antibiotic prescribing are upper respiratory tract infections (URTIs), which are in more than 90% caused by viruses (4). The URTIs are clinically presented with a spectrum of different symptoms and different intensity of disease from mild catarrhal symptoms of upper respiratory tract, flu symptoms, streptococcal angina, laryngotracheobronchitis to symptoms of lower respiratory tract (5). Only 5 to 15% cases of tonsillopharyngitis are caused by beta-hemolytic *Streptococcus* A (BHSA), which (1, 6-10), according to Evidence Based Medicine (EBM) and national and international guidelines, require using antibiotics to shorten the duration of the disease and reduce the possibility of complications (6,7,12).

Guidelines of an interdisciplinary team for control of antibiotic resistance (''ISKRA'') for antibiotic prescribing for tonsillopharyngitis are based on Centor clinical criteria (6). According to ISKRA guidelines for patients' infections with Centor score 2-4, the bacterial test is recommended (rapid strep test or culture), and prescribing antibiotic if a result is positive (6). The reason for recommendation for confirming clinical diagnosis with microbiological tests is based on results of studies, which estimate sensitivity and specificity of clinical diagnosis of streptococcal angina to 55-75%. However, BHS-A cultivation and rapid test do not have sensitivity and specificity of 100% either. A BHS-A carriers can be registered in up to 40% of healthy persons, which reduces specificity of BHS-A positive test in cases of mild presentation of clinical status of acute sore throat (6).

In Croatia according to data from 2017 there were 2313 general practitioners on the population of 4,124,531 inhabitants, half of them specialists of family medicine (1115). One team is approximately in charge of 1,802 patients (13). Only primary care physicians (also those on duty during weekends) and emergency physicians can prescribe antibiotics in Croatia, and that prescription makes 92% of complete consumption of antibiotics (14). Analysing the data from wholesale pharmacies in 2016, it was 21,57 of defined daily dose (DDD/DDT), and it is higher than National Health Insurance company data (NHI – ''HZZO'') (20,73 DDD/TID) (4). Antibiotic consumption in year 2017 according to wholesale pharmacies data was 21.91 DDD/TID comparing to HZZO data of 20.48 DDD/TID. Although patients in Croatia with health insurance can get all antibiotics without additional paying, some patients use private prescriptions, and that is the reason for different data between wholesale pharmacies and NHI.

A survey conducted in Croatia in 2007 by Botica Vrca et al. analysed 689 visits to general practice because of URTIs. Results showed that antibiotics had been prescribed in 44.7% of cases. Antibiotics were prescribed in 81.9% of visits because of tonsillopharyngitis with Centor score 3 and 4, and in 49,6% of visits with Centor score 1 and 2 (12).

The aim of the survey was to analyse antibiotic prescribing for URTIs in general practice. Specific aims were to define the diagnostic and therapeutic procedures that general practitioners use in the process of care, and also a share of specific antibiotics. The hypothesis was that general practitioners prescribed antibiotics for URTIs rationally.

PATIENTS AND METHODS

Patients and study design

A cross-sectional study was conducted with participation of 17 general practices. The participants in this study were general practitioners (GPs) working in Croatia, who are also members of The Group for Informing about Primary Care Work''. The participants were collected using a mailing list of the Group. A total of GPs had been contacted, 27 of them agreed to participate in study and they had received a specially created questionnaire and instructions for the study. A total of 17 GPs completed the study and collected necessary data. The study had been conducted in the periods of one week for three consecutive months (October, November and December 2017). Those specific months had been chosen because of high prevalence of respiratory infections, and at the same time the period of highest prevalence of flu had to be avoided. The framework of the study was an encounter (visit) – initial or control in general practice. Phone consultations, electronic advices (e-mail) and home visits had been exclu-

ded, and also patients with lower respiratory tract infections such as asthma, chronic bronchitis or pneumonia. The study comprised 709 patients. The study protocol and materials were approved by the Ethics Committee of the county health centre (”Dom zdravlja Zagrebačke županije”).

Methods

Symptoms of URTIs were coded using the International Classification of Primary Care (ICPC-2) (11): fever (A03), weakness (A04), headache (R01), cough (R05), nose symptoms (R08), throat symptoms (R21), ear pain (H01) and eyes symptoms (F29). According to coded symptoms – reasons for encounter and registered clinical status, two independent doctors classified cases using Centor criteria (age, exudate or swelling on tonsils, swollen anterior cervical lymph nodes, temperature >38 ˚C) classifying cases/patients based on Centor score. Data collected during the study were analysed in Excel, and presented in absolute number (n) and percentage (%). A method of descriptive analysis was used. In case of more than one visit during the same episode of URTI, each of them was analysed separately and marked as initial or control visit.

Statistical analysis

The analysis between groups was performed using χ^2 test. Logistic regression analysis was used for presenting the influence of one or more independent variables on antibiotic prescribing, and $p < 0.05$ was used for the level of statistical significance.

RESULTS

During the study period GPs registered 749 visits due to URTIs, and 40 of them were excluded because of concurrent lower RTIs. A total of 392 (55.3%) visits from 709 patients in total were female. Analysing the age of the patients who visited their GP in this study, 485 (68.4%) were 7-45 years old.

There were 521 (73.4%) initial visits, and (188) 26.5% control visits; 145 (27.8%) of initial visits and 58 (30.9%) of control visits were registered on Mondays; 157 (83.5%) control visits were made by patients whose initial visits were also in their general practice. The reason for attending the control visit was in 77.1% of cases control clinical examination, and in 15.4% it was test results (x-ray or microbiological test results). The data about the number of patients who entered health system through other ‘’entrances’’ (emergency units, otorhinolaryngology, infectiology) were not registered.

A total of 228 (43.8%) patients had symptoms 1-2 days before initial visits to GPs, and 100 (53.2%) had symptoms 3-5 days before control visits to GPs. The most common reasons for initial visit to GPs were symptoms connected to throat (R21) in 371 (71.2%), cough (R05) in 296 (56.8%), fever (A03) in 271 (52%) and symptoms connected to nose (R08) in 257 (49.3%) cases. Symptoms connected to throat were reported less during control visits (Table 1).

Table 1. Symptoms presented during 521 initial and 188 control visits

Symptoms (ICPC 2 code)	No (%) of patients	
	Initial visit	Control visit
Sore throat (R21)	371 (71.2)	106 (56.4)
Axillar temperature 37-38 °C (A03)	163 (31.3)	57 (30.3)
Axillar temperature >38 °C (A03)	108 (20.7)	34 (18.1)
General weakness (A04)	121 (23.0)	52 (27.7)
Running nose (R08)	257 (49.3)	74 (39.4)
Cough (R05)	296 (56.8)	112 (59.6)
Eyes symptoms (F29)	27 (5.2)	6 (3.2)
Headache (R01)	105 (20.2)	21 (11.2)
Ear symptoms (H01)	58 (11.1)	12 (6.4)

During initial visits 521 GPs registered 570 procedures, of which 311 (54.6%) included advice about symptomatic care and 176 (30.9%) were antibiotic prescribing. During control visits 203 procedures were performed by 188 GPs, and 96 (47.2%) offered advice about symptomatic procedures and 69 (34%) were antibiotic prescribing (Table 2).

Table 2. Procedures performed by general practitioners (GPs) during the process of care for 521 initial and 188 control visits

GPs procedure	No (%) of visits	
	Initial visits	Control visits
Advice only	311 (54.6)	96 (47.2)
Referred to laboratory tests	63 (11.1)	16 (7.8)
Referred to microbiological tests	4 (0.7)	2 (1.0)
Rapid strep test on Streptococcus done	0 (0.0)	0 (0.0)
Referred to X-Ray	7 (1.2)	4 (2.0)
Referred to secondary care examination	2 (0.3)	4 (2.0)
Antibiotic prescribed	176 (30.9)	69 (34.0)
Other*	7 (1.2)	12 (6.0)

In cases of URTIs antibiotics were prescribed to 245 (34.6%) patients. Most of the patients who did not get antibiotics had infections with Centor score 1, 237 (68.7%); 38 (21.6%) patients with

prescribed antibiotic had infections with Centor score 3 and 35 (19.9%) Centor score 4 (Table 3).

Table 3. Clinical status of 709 patient visits according to Centor score and antibiotics prescription

Centor score	No (%) of patients		p
	Antibiotic (n=245)	No antibiotic (n=464)	
Initial visit	176 (71.8)	345 (74.4)	0.527
0	6 (3.4)	6 (1.7)	0.372
1	52 (29.5)	237 (68.7)	0.000
2	45 (25.6)	88 (25.5)	0.927
3	38 (21.6)	10 (2.9)	0.000
4	35 (19.9)	4 (1.2)	0.000
Control visit	69 (28.2)	119 (26.0)	0.527
0	7 (10.1)	6 (5.0)	0.303
1	29 (42.0)	80 (67.2)	0.001
2	15 (21.7)	27 (22.7)	0.975
3	12 (17.4)	4 (3.4)	0.002
4	6 (8.7)	2 (1.7)	0.055

Logistic regression analysis showed no statistical significance in antibiotic prescribing in relation to nonclinical parameters (gender, age, school and working status of patients) except positive influence of the day of the week (Monday) (Table 4).

Table 4. Logistic regression – impact of non-clinical parameters to antibiotic prescribing during 709 visits

Parameter	No (%) of patients	OR [CI]	p
Gender			
Male	317 (44.7)	0.83 [0.60-1.13]	0.231
Female	392 (55.3)	0.83 [0.60-1.13]	0.231
Age			
<6 years	62 (8.8)	1.52 [0.90-2.57]	0.125
7-20 years	236 (33.3)	0.98 [0.71-1.37]	0.926
21-45 years	249 (35.1)	0.99 [0.72-1.38]	0.994
46-70 years	127 (17.9)	0.77 [0.51-1.17]	0.221
>71 years	35 (4.9)	1.13 [0.56-2.28]	0.743
Status of the education/employment			
Students	301 (42.5)	1.11 [0.81-1.51]	0.524
Employed	268 (37.8)	0.86 [0.62-1.19]	0.360
Unemployed	139 (19.6)	1.08 [0.73-1.59]	0.696
Primary school	68 (9.6)	0.83 [0.49-1.43]	0.500
High school	265 (36.1)	0.91 [0.66-1.26]	0.569
University	89 (12.6)	1.07 [0.67-1.71]	0.767
Days (in the week)			
Mondays	203 (28.6)	1.65 [1.18-2.31]	0.003
Tuesdays	128 (18.1)	0.83 [0.55-1.26]	0.385
Wednesdays	151 (21.3)	0.70 [0.47-1.04]	0.078
Thursdays	109 (15.4)	0.87 [0.57 – 1.36]	0.560
Fridays	118 (16.6)	0.97 [0.64-1.47]	0.869

The most prescribed group of antibiotics during first visits was the penicillin group, 133 (74.8%) patients, followed by macrolides, 31 (17.6%) and cephalosporins, seven (4.0%) patients. Phenoxymethylpenicillin was the most prescribed among penicillin antibiotics, 47 (26.7% of totally prescribed antibiotics), followed by amoxicillin, 46 (26.1%), and amoxicillin + clavulanic acid, 40 (22.7%). Azithromycin was the most prescribed antibiotic among macrolides, in 27 (87%), followed by clarithromycin, in four (13%) cases; cephalexin was the most prescribed among cephalosporins, in four (57%), followed by cefuroxime, in three (43%) cases. During control visits the most prescribed antibiotic was amoxicillin + clavulanic acid, in 26 (37.7%) cases (Table 5).

Table 5. Antibiotics prescribed (J01) according to the Anatomical Therapeutic Chemical Classification (ATC) during 176 initial and 69 control visits

Antibiotic prescribed	No (%) of patients	
	Initial visit	Control visit
Beta-lactam penicillin	133 (75.5)	49 (71)
Amoxicillin	46 (26.1)	17 (24.6)
Amoxicillin +clavulanic acid	40 (22.7)	26 (37.7)
Phenoxyimethylpenicillin	47 (26.7)	6 (8.7)
Cephalosporins	7 (4.0)	6 (8.7)
Macrolides and lincosamides	33 (18.7)	14 (20.2)
Tetracyclines	3 (1.7)	0 (0.0)
Quinolones	0 (0.0)	0 (0.0)
Total	**176**	**69**

DISCUSSION

This showed that most of the visits to GPs because of URTIs were the first or initial. The symptoms persisted on average 1-2 days before initial visits to GPs. According to the literature the percentage of initial visits was from 82% in 2007 in Croatia up to 95% in Norway (12,15). The higher frequency of control visits is a result of some GP's procedures, for example referring to diagnostic tests and consultations, recommendation for control examination. Patients visited their GPs during the first 2 days after onset of symptoms in 45.8% cases, and in Croatia in 2007 most of the visits to GPs were on third to fifth day of the disease. This difference can be explained with administrative reasons, for example the need for GPs' documents because of absence from work or school (12).

The reasons for initial visits to GPs in our study were similar to the results found in other studies, in the USA the most common reasons for initial visits to GPs were cough (64%), sore throat (55%) and nose symptoms (47%) (15). In 83.5% of cases of control visits, initial visit was also at GPs. The URTIs usually lasted short, for up to 5 days (5), and after they were over the patients did not go to GPs. According to the literature, initial visits can be made to emergency unit, infectiology, otorhinolaryngology, paediatrics or other GPs (12,16,17). The data from the literature can vary depending on possibilities of entering the

health system and also profile of health care providers that can prescribe antibiotics.

Antibiotics were prescribed for URTIs in 34.6% of visits in our study. The frequency of antibiotics prescribed for URTIs varies from 14% in the Netherlands (18), 24.9% in Sweden (19), 24.9% in Germany (20), 33.5 - 34.2% in Norway (15,21), 44.7% in Croatia (2007.g) (12), 59.3% in Denmark, 75.8% on Iceland (22), in the USA 77.5% (23). Antibiotics are prescribed during first visits for tonsillopharyngitis with Centor score 1 and 2 in 22.8% of cases, and in Croatia in 2007 they were prescribed in 49.6% of cases for the same score of tonsylopharyngitis. That percentage was interpreted as unnecessary antibiotic prescribing (12). For tonsillopharyngitis with Centor score 3 and 4 antibiotics were prescribed in 85.1% of cases in comparison with 81.9% in 2007 (12). In Australia antibiotics are prescribed for tonsillitis in 94% of cases (24), in Iceland in 58.7% and in Danmark in 21% (22,25).

The lower percentage of antibiotics prescribed for infections with Centor scores 1 and 2 in comparison with 2007 can be explained with the implementation of national ISKRA guidelines for sore throat and results of primary prevention – better informing and higher awareness of unnecessary antibiotic prescribing. It resulted with lower level of patients' pressure on physicians for antibiotic prescribing.

Performing the microbiological tests in primary care often have obstacles - travelling to hospitals, sending of materials, waiting for the results. Rapid strep test is not paid by the national health insurance company. The studies confirmed that in the USA physicians used rapid strep test on 18% of patients with tonsillopharyngitis, 8% of patients were sent to check CRP and 6% were referred for microbiological tests (16). The studies also showed the important influence of laboratory test results on antibiotics prescribing. The CRP value is connected to significant decrease of antibiotics prescribing (10, 26-28), but also to more hospital admittance when CRP is pathological (26). According to Spanish STREP study, low values of CRP and negative rapid strep tests result also with a decrease of antibiotics prescribing (29).

Logistic regression analysis on influence of nonclinical variables showed that gender, age, school and working status do not have any influence on incidence of antibiotics prescribing, and literature showed that the age was a risk for antibiotic prescribing. According to the literature, the lowest probability for antibiotic prescribing is to persons older than 80 and children younger than 6 (30). Analysing nonclinical variable – the day of the week – GPs most often prescribed antibiotics on Mondays, which is different from data from the literature, e. g. Fridays (15,31), and Wednesdays in Croatia (12).

The most often prescribed antibiotics during the first visits were phenoxymethylpenicillin, amoxicilin and amoxicilin + clavulanic acid. Amoxicillin + clavulanic acid was the most often prescribed antibiotic during control visits. The studies have shown that the most often prescribed antibiotic for respiratory infections in Croatia and Spain is amoxicillin + clavulanic acid (12,30), in Sweden and Denmark it is phenoxymethylpenicillin (16,25,32,33), in Netherlands amoxicillin (17), in the USA azithromycin. In Croatia prescribing broad-spectrum penicillin antibiotics continues to fall for the fifth consecutive year, which is not the case with their combination with inhibitors of beta-lactamase, which remain the most often prescribed antibiotics (4,14). Rare use of phenoxymethylpenicillin is not in accordance with the guidelines for the treatment of respiratory infections, which indicates that the current practice of antibiotic prescribing has to be changed (25).

A limiting factor of this study is the prospective collecting of the data during visits and not electronic database, so limited time of the visit and physicians' overload could lead to missing some visits because of URTIs.

In conclusion, this study showed that prescribing of antibiotics in tonsillopharyngitis within low-risk patients was high. Our study showed that swabbing was not a common practice. General practitioners prescribe antibiotics in higher proportion than recommended by Evidence Based Medicine and professional criteria. Comparing to the study from 2007 a lower percentage of antibiotic prescribing for acute respiratory infections has been registered, but there is still a need for improvement.

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Conflicts of interest: None to declare.

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