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Original study
Originalni naučni rad
UDK 616.2-022.1-053.2:615.33-03
DOI: 10.2298/MPNS1410282T

ANALYSIS OF ANTIBIOTIC CONSUMPTION FOR TREATING RESPIRATORY TRACT INFECTIONS IN CHILDREN AND COMPLIANCE WITH THE NATIONAL CLINICAL GUIDELINES

ANALIZA POTROŠNJE ANTIBIOTIKA ZA LEČENJE INFEKCIJA RESPIRATORNOG TRAKTA U DEČJOJ POPULACIJI I USKLAĐENOSTI SA NACIONALNIM VODIČIMA DOBRE KLINIČKE PRAKSE

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Summary

Introduction. Respiratory infections are the most common infections in children. The aims of the study were to analyze the use of antibiotics for respiratory infections in the period 2008 – 2010 in children's population in region of Niš and to estimate the rational use of antibiotics in relation to the recommendations of the National Guidelines for physicians in primary care. **Material and methods.** Data source was a Pharmacy Niš database. Antibiotics prescriptions were selected for the following diagnoses: H65-H75 (acute otitis media, mastoiditis), J01 (acute sinusitis), J02-J03 (tonsillopharyngitis), J12-J18 (community acquired pneumonia), J20 (acute bronchitis), J32 (chronic sinusitis), J42 (chronic bronchitis). Antibiotic consumption was expressed in defined daily dose/1000 inhabitants/day. **Results.** The most widely prescribed antibiotic for the treatment of upper respiratory tract infections in children during the three years was amoxicillin (34.63; 32.50 and 31.00 defined daily dose/1000 inhabitants/day in 2008, 2009 and 2010, respectively). In the treatment of infections of the middle ear and mastoid, the combination of amoxicillin and clavulanic acid, was the most prescribed antibiotics (60% of total consumption of antibiotics for this indication). Azithromycin was the most widely prescribed antibiotic for the treatment of lower respiratory tract infections in children during the observed period (6.92; 8.20 and 7.18 defined daily dose/1000 inhabitans/day in 2008, 2009 and 2010, respectively). **Conclusion.** Recommendations of national guidelines are not complied with the treatment of upper and lower respiratory infections in the children population in region of Niš. This could be a sign of potentially irrational use of antibiotics that need to be further examined. Education of physicians can influence irrational use of antibiotics.

Key words: Anti-Bacterial Agents; Respiratory Tract Infections; Child; Physician's Practice Paterns; Practice Guideline; Drug Utilization

Sažetak

Uvod. Infekcije respiratornog sistema predstavljaju najčešće infekcije kod dece. Ciljevi ovog rada jesu analiza potrošnje antibiotika u lečenju infekcija gornjih i donjih respiratornih puteva kod dece u Nišavskom okrugu i procena racionalnosti upotrebe antibiotika u odnosu na preporuke Nacionalnog vodiča za lekare u primarnoj zdravstvenoj zaštiti. **Materijal i metode.** Kao izvor podataka korišćena je baza podataka Apoteke Niš za period 2008−2010. godine. Selektovani su svi izdati recepti antibiotika propisani deci starosti 0−19 godina za terapiju infekcija respiratornog trakta uključujući infekcije srednjeg uva ((H65-H75 (akutni otitis media i mastoiditis), J01 (akutni sinuzitis), J02-J03 (tonzilofaringitis), J32 (hronični sinuzitis) (J12-J18 (blaga do umerena pneumonija izazvana vanbolničkim uzročnikom), J20 (akutni bronhitis), J42 (hronični bronhitis)). Potrošnja je izražena u definitivnoj dnevnoj dozi/1 000 stanovnika/dan. **Rezultati.** Najpropisivaniji antibiotik za terapiju infekcija gornjeg respiratornog trakta kod dece u posmatranom periodu bio je amoksicilin (34,63; 32,5 i 31 definitivnoj dnevnoj dozi/1 000 stanovnika/dan tokom 2008, 2009. i 2010. godine). Za terapiju infekcije srednjeg uva i mastoidnog nastavka najčešće je korišćena kombinacija amoksicilina i klavulanske kiseline (60% ukupne potrošnje svih antibiotika za ovu indikaciju). Azitromicin je bio najpropisivaniji antibiotik za terapiju infekcija donjeg respiratornog trakta kod dece tokom posmatranog perioda (6,92; 8,2 i 7,18 definitivnoj dnevnoj dozi/1 000 stanovnika/dan tokom 2008, 2009. i 2010. godine). **Zaključak.** Preporuke nacionalnih vodiča nisu poštovane ni u slučaju terapije gornjih ni donjih respiratornih infekcija kod dece u Nišavskom regionu. To može biti znak potencijalno neracionalne upotrebe antibiotika koju je potrebno dodatno istražiti. Dodatna edukacija lekara mogla bi uticati na smanjivanje neracionalne upotrebe antibiotika.

Ključne reči: Antibiotici; Infekcije respiratornog trakta; Dete; Lekarska praksa; Vodiči; Korišćenje lekova

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Acknowledgement

This work has been supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia, Project No. 41012, and Project No. 175035, 2011-2014.

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Abbreviations

RTIs – respiratory tract infections
WHO – World Health Organization
ICD – International Classification of Diseases
ATC – anatomical therapeutic chemical
DDD – defined daily dose
DID – defined daily doses per 1000 inhabitants per day
INN – international non-property name
H65-H75 – acute otitis media, mastoiditis
J01 – acute sinusitis
J02-J03 – tonsillopharyngitis
J32 – chronic sinusitis
J12-J18 – mild to moderate community-acquired pneumonia
J20 – acute bronchitis
J42 – chronic bronchitis

Introduction

Respiratory tract infections (RTIs) are the most frequent infections in all age groups of patients. According to the World Health Organization (WHO) Report for 2002, RTIs were reported to be the cause of 3.9 million deaths per a year [1]. The frequency of RTI in an adult is 3–5 episodes per a year, and even more in children. The frequency of RTI and the clinical state of a child with RTI depend on anatomical and functional characteristics of the organism, immunological state, age, gender, nutritional status of the child, as well as on the socio-economic factors [2–4].

The most extensive study on RTIs and associated risk factors in children was performed in Cleveland in 1964. The study results suggested that the frequency of RTI depended on the child's age. The authors emphasized a wide range of episodes of RTI in "healthy" children, the average number of episodes being 7.4 per a year in five-year-old children and the number ranging from 0 to 18. Assuming that an episode usually lasts one to two weeks, a five-year old child with 18 episodes of RTIs can be ill for 4.5-9 months per a year. According to the same study, the frequency of RTI is affected by the number of family members and the risk increases twice to eight times when the children attend kindergartens [5]. Fortunately, RTIs do not cause a high mortality rate; however, the morbidity rate is very high. Besides being the most frequent infections at children's age, these infections are the most frequent cause of children visiting general practitioners or paediatricians as well as of their hospitalization worldwide [6]. According to the data of the Institute for Public Health of Serbia for 2011, the total number of respiratory system diseases (diagnoses ICD-10, J00 – J99 according to the International Classification of Diseases, 10th Revision – (ICD-10) was over 1.6 million in children younger than age 6 years, that accounting for 55% of all recorded diseases, states and injuries.

At the same time, RTIs diagnosed in schoolchildren aged from 7 to 9 accounted for 48% of all recorded diseases, states and injuries in this population group [7].

Upper respiratory tract infections are more frequent than lower respiratory tract ones, representing 90% of all RTIs [8]. They were also more frequent in children and adolescents in Serbia, where tonsillopharyngitis accounted for 51% of all diseases in 2011 [7].

RTIs in children are caused by viruses, bacteria and other agents in 75, 15 and 10% of cases, respectively [9]. Therefore, the first line therapy of RTIs should be symptomatic therapy, while antibiotics should be the second line therapy. However, RTIs in children are the most common cause for prescribing antibiotics in the whole world. Prescriptions for antibiotics in treatment of RTIs amount to 75% of all prescriptions at the primary health care level [10, 11]. Concurrently, more than 50% of all prescriptions are for upper RTIs. Consequently, drug use in therapy of RTIs is often irrational. Unnecessary antibiotic treatment results in a number of unintended consequences, especially in the increase of bacterial resistance and enormous financial expenses. The most abused administration of antibiotics is in unnecessary treatment of viral infections, particularly in children. An additional problem is the consequent use of broad-spectrum antibiotics and the new generation antibiotics, which are more expensive [10–12]. Antibiotics should be chosen based on the identification of microbial pathogens, determination of antibiograms, pharmacokinetics of the drug, the age and general condition of the child, previous therapy, a possible allergic reaction to the applied antibiotic and drug prices [13].

The Ministry of Health of the Republic of Serbia adopted two guidelines for antibiotic prescribing in general practice within the primary health care of children and adults. The Guideline "The Selection and Use of Antibiotics in General Practice" [14] recommends therapy for several different infections, including RTIs and otorhinolaryngeal infections. It discourages administration of antibiotics in therapy of upper RTIs and mild symptoms of lower RTIs. Antibiotics should be used in therapy of community-acquired pneumonia; amoxicillin and azithromycin in children younger and older than age 5 years, respectively. Recommendations for therapy of acute otitis media are given in two guidelines "The selection and Use of Antibiotics in General Practice" and "Otitis Media" [15].

The aims of this study were to analyze antibiotic consumption in treatment of upper and lower RTIs in children population in region of Niš, and to analyze compatibility of the study results regarding drug consumption with the national guideline recommendation for treatment of RTIs.

Material and Methods

The source of data on outpatient antibiotic consumption issued on prescription was the anonymous

electronic database of Pharmacy Niš for the period from 2008 to 2010. The base anonymity included the anonymity of the patient, doctor and pharmacy. Criteria for database search were the patient's year of birth, the code of disease (ICD-10) for which antibiotic was issued, commercial drug name, the anatomical therapeutic chemical (ATC) code of drug, the number of issued packages, date of drug issue, etc. Criteria for data selection were the following disease codes: H65-H75 (acute otitis media, mastoiditis); upper RTIs: J01 - acute sinusitis, J02-J03 – tonsillopharyngitis, J32 - chronic sinusitis; lower RTIs: J12-J18 – mild to moderate community-acquired pneumonia, J20 - acute bronchitis, J42 - chronic bronchitis. The data on issued antibiotics were selected for each diagnosis according to the ATC classification: J01A (Tetracyclines), J01C (beta-lactam antibiotics), J01D (cephalosporins), J01E (sulphonamides and trimethoprim), J01F (macrolides, lincosamides), J01M (hinolons). Antibiotics consumption was followed in the period from 2008 to 2010.

Defined daily dose (DDD) was used in expression of antibiotics consumption. The DDD was suggested by the WHO as the *"*assumed average maintenance dose per day for a drug used for its main indication in adults". The unit DDD is an average dose for adult of 70 kg weight and it is independent of price and dosage form. It enables the researcher to assess trends in drug consumption and to perform comparisons between population groups. The DDD values were taken from the WHO web site [16]. Nowadays, drug consumption is expressed by DDD per 1000 inhabitants per a day (DDD/1000 inhabitants/day (DID)). The following formula was used to calculate drug consumption:

DID = (the amount of drug used in one year (mg) x 1000)/365 x the number of inhabitants x DDD (mg)

Antibiotic consumption in our study was expressed in DID for each antibiotic according to the international non-property name (INN), diagnosis, patient's age and the year of drug prescribing. The results were expressed as aggregated data for the children and adolescents aged 0-19 years. Due to the differences in guideline recommendations regarding treatment of community-ac-

Table 1. Consumption (expressed in DDD/1000 inhabitants/day) of the antibiotics groups (according to ATC classification) for the outpatient treatment of respiratory infections in children population during the period 2008 – 2010 year in region of Niš

Tabela 1. *Potrošnja (izražena u DDD/1 000 stanovnika/dan) grupe antibiotika (prema ATC klasifikaciji) za vanbolničku terapiju respiratornih infekcija kod dece u periodu 2008–2010. godine u Nišavskom regionu*

		Antibiotic consumption (DID)/*Potrošnja antibiotika (DID)*								
		Upper RTIs *Infekcije gornjeg respiratornog trakta* (J01, J02, J03, J32)			Complications of upper *Komplikacije infekcija gornjeg respiratornog trakta* RTIs (H65-H75)			Lower RTIs *Infekcije donjeg respiratornog trakta* (J12-J18, J20, J42)		
ATC classification *ATC klasifikacija*	Drug group *Grupa lekova*	2008	2009	2010	2008	2009	2010	2008	2009	2010
J01AA	tetracyclines	0.173	0.183	0.155	0.001	0.000	0.000	0.017	0.020	0.021
J01CA	broad spectrum penicillin	34.628	32.603	31.003	1.002	0.710	0.602	1.233	0.906	1.378
J01CE	beta-lactamase sensitive penicillin	10.868	10.598	7.520	0.041	0.029	0.040	0.327	0.264	0.237
J01CR	penicillin in combination with inhibitors of beta- lactamase	25.282	26.727	22.782	3.343	2.812	3.277	1.967	2.264	2.566
J01DB	1st generation of cephalosporins	13.893	12.408	11.669	0.001	0.000	0.001	1.214	1.168	1.236
J01DC	2nd generation of cephalosporins	3.439	3.863	3.170	0.342	0.428	0.648	1.368	1.888	1.484
J01DD	3rd generation of cephalosporins	5.612	6.829	5.893	0.222	0.257	0.241	6.409	6.422	5.711
J01EE	sulfonamids with thrimethoprime	1.382	1.114	0.811	0.029	0.014	0.009	0.075	0.067	0.059
J01FA	macrolides	26.971	29.317	23.338	0.209	0.382	0.228	11.466	12.564	10.605
J01FF	lincosamides	0.196	0.105	0.250	0.008	0.002	0.009	0.023	0.023	0.043
J01MA	fluoroquinolones	0.001	0.001	0.001	0.000	0.009	0.017	0.008	0.012	0.009
	Total/*Ukupno*	122.444	123.750	106.591	5.197	4.644	5.072	24.107	25.599	23.350

*DDD - definisana dnevna doza, **ATC - anatomsko-terapeutsko-hemijska, DID - DDD/1 000 stanovnika/dan*

Table 2. Consumption (expressed in DDD/1000 inhabitants/day) of the specific antibiotics (INN) for the outpatient treatment of respiratory infections in children population during the period 2008 – 2010 year in region of Niš
Tabela 2. *Potrošnja (izražena u DDD/1000 stanovnika/dan) pojedinačnih antibiotika (INN) za vanbolničku terapiju respiratornih infekcija kod dece u periodu 2008–2010. godine u Nišavskom regionu*

	Antibiotic consumption (DID)/*Potrošnja antibiotika (DID)*								
	Upper RTIs *Infekcije gornjeg respiratornog trakta* (J01, J02, J03, J32)			Complications of upper RTIs/*Komplikacije infekcija gornjeg respiratornog trakta* (H65-H75)			Lower RTIs *Infekcije donjeg respiratornog trakta* (J12-J18, J20, J42)		
INN	2008	2009	2010	2008	2009	2010	2008	2009	2010
Doxycycline	0.173	0.183	0.155	0.001	0.000	0.000	0.017	0.020	0.021
Amoxicillin	34.628	32.603	31.003	1.002	0.710	0.602	1.233	0.906	1.378
Phenoxymethylpenicillin	10.868	10.598	7.520	0.041	0.029	0.040	0.327	0.264	0.237
Amoxicillin. clavulanic acid	25.282	26.727	22.782	3.343	2.812	3.277	1.967	2.264	2.566
Cephalexin	12.538	11.279	10.442	0.001	0.000	0.001	1.153	1.088	1.145
Cefadroxil	1.355	1.129	1.227	0.000	0.000	0.000	0.061	0.080	0.091
Cefuroxime	0.194	0.570	0.668	0.000	0.000	0.000	0.150	0.237	0.296
Cefprozil	3.244	3.293	2.502	0.342	0.428	0.648	1.218	1.650	1.188
Cefixime	5.612	6.829	5.893	0.222	0.257	0.241	6.409	6.422	5.711
Thrimethoprim sulfamethoxazole	1.382	1.114	0.811	0.029	0.014	0.009	0.075	0.067	0.059
Erytromycin	10.865	11.405	10.066	0.039	0.046	0.005	1.512	1.280	1.600
Midecamycin	0.000	0.000	0.299	0.000	0.000	0.000	0.000	0.000	0.000
Roxithromycin	0.740	0.703	0.579	0.002	0.001	0.003	0.116	0.103	0.097
Clarithromycin	7.857	7.518	4.027	0.080	0.236	0.142	2.921	2.979	1.723
Azithromycin	7.509	9.692	8.366	0.088	0.099	0.079	6.917	8.203	7.185
Clindamycin	0.196	0.105	0.250	0.008	0.002	0.009	0.023	0.023	0.043
Ofloxacin	0.001	0.001	0.001	0.000	0.001	0.000	0.000	0.000	0.000
Ciprofloxacin	0.000	0.000	0.000	0.000	0.008	0.017	0.008	0.012	0.009
Total/*Ukupno*	122.444	123.750	106.591	5.197	4.644	5.072	24.107	25.599	23.350

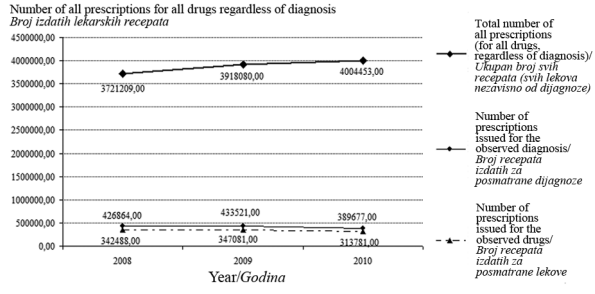
DID - DDD/1 000 stanovnika/dan

quired pneumonia in children under and above 5 years of age, subanalaysis was done for the diagnosis J12 – J18 for these two clusters of patients [14]. The number of inhabitants was taken from census 2002 for the population aged 0-19 years (80424) and the two mentioned clusters (16289 (0-4 years) and 64135 (5-19 years) [17]. Data on the number of inhabitants for each of observed years were not used in order not to compromise the accuracy of results.

Results

A low reduction in antibiotic prescribing was observed during the period 2008-2010 by comparing the total number of prescriptions (regardless of diagnosis) and the number of antibiotics prescribed for the observed respiratory diagnoses **(Graph 1).** The share of antibiotic prescriptions issued for RTI in the total number of issued prescriptions was 9.20%, 8.86% and 8.23% in 2008, 2009 and 2010, respectively.

The most widely prescribed antibiotics in treatment of upper RTIs was broad-spectrum penicillin followed by macrolides and penicillin in combination with inhibitors of beta-lactamase. These three groups of antibiotics accounted for more than 70% of total antibiotic consumption in the three observed years. The total antibiotic con-



Graph 1. The total number of the medical prescriptions in region of Niš for all medications and selected respiratory infections issued between 2008-2010 year
Grafikon 1. *Ukupan broj lekarskih recepata u Nišavskom regionu za sve dijagnoze i posmatrane dijagnoze respiratornih infekcija izdatih u periodu 2008−2010. godine*

sumption was 122.444, 123.750 and 106.591 DID in 2008, 2009 and 2010, respectively (**Table 1**).

The most widely prescribed antibiotic in therapy of upper RTIs according to INN was amoxicillin throughout the observed period, being 34.628, 32.603 and 31.003 DID in 2008, 2009 and 2010, respectively. The second place was taken by amoxicillin in combination with clavulanic acid. The share of amoxicillin, alone and in combination with clavulanic acid, accounted for almost 50% of the total antibiotic consumption. The consumption of almost all antibiotics was constant in the observed period, except for clarithromycin, whose consumption in 2010 was reduced by almost 50% in comparison with the consumption in 2009 (**Table 2**).

The most prescribed antibiotic in therapy of otitis media throughout the observed period was amoxicillin in combination with clavulanic acid. The share of this combination accounted for more than 60% in the total antibiotic consumption in therapy of otitis media in each observed year. Amoxicillin was on the second place, 1.002, 0.710 and 0.602 DID in 2008, 2009 and 2010, respectively (**Table 2**).

Antibiotics most widely prescribed in treatment of lower RTIs were macrolides. The consumption of cephalosporins, 3rd generation was less than half of macrolides consumption, while prescribing of other antibiotics was marginal. The total antibiotic consumption in treatment of lower RTIs was 24.107, 25.599 and 23.350 DID in 2008, 2009 and 2010, respectively (**Table 1**).

The most prescribed antibiotic by INN in therapy of lower RTIs throughout the observed period was azithromycin, 6.917, 8.203 and 7.185 DID in 2008, 2009 and 2010, respectively. Cefixime was on the second place. These two antibiotics accounted for more than 50% in the total antibiotic consumption in therapy of lower RTIs during the observed period (**Table 2**).

Some of the observed antibiotics were not prescribed for certain indications during the study period (e.g. midecamycin). Several antibiotics were not prescribed in each of observed years (e.g. doxycycline, cephalexin, ofloxacin) (**Table 2**).

The results of subanalaysis of antibiotic consumprion in treatment of community-acquired pneumonia in children under and above 5 years of age are given in **Graph 2**.

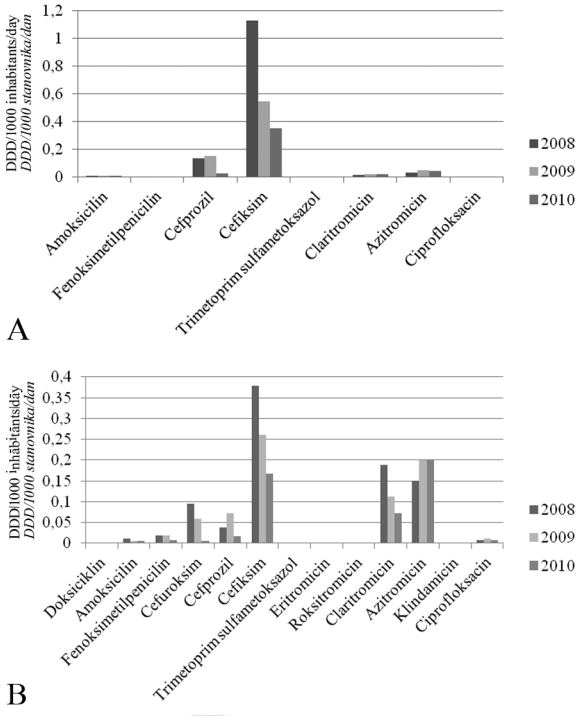
Cefixime and cefprozil were the most frequently prescribed antibiotics in treatment of community-acquired pneumonia in children 0-4 years old. Cefixime was also the most frequently prescribed antibiotic in therapy of observed indications in the population 5-19 years old in 2008 and 2009 (0.38 and 0.26 DID, respectively); but, in 2010, it was azithromycin (0.20 DID).

Discussion

The results of our study showed that the number of prescriptions for antibiotics given for RTIs decreased in 2010 comparing to 2009, in spite of increase in the total number of prescriptions regardless of diagnoses issued during the period 2008-2010.

Amoxicillin, alone or in combination with clavulanic acid, was the most widely prescribed antibiotic in therapy of upper RTIs throughout the observed period. The results showed that 12% of children consumed antibiotics prescribed for upper RTIs in region of Niš every day in 2008 and 2009, while it was 10% in 2010. Clinical practice showed non-adherence to National guidelines which recommended not prescribing antibiotics for upper RTIs, except for sinusitis and severe clinical state of the patient when the drug of choice should be amoxicillin. Serbian national guidelines are in line with the guidelines of the National Institute of Health and Care Excellence of Great Britain, which recommend the strategy of delayed prescribing [18].

Previous studies showed irrational antibiotic consumption in upper RTIs [11, 19]. As many as 46% of children with upper RTIs consumed an antibiotic in spite of its lack of efficacy in the therapy of upper RTIs. It was observed that antibiotics were more prescribed to children aged from 5 to 11 years



Graph 2. Consumption (expressed in DDD/1000 inhabitants/day) of the specific antibiotics (INN) for the outpatient pneumonia in children younger than 5 (A) and children older than 5 years (B)

Grafikon 2. *Potrošnja (izražena u DDD/1000 stanovnika/dan) pojedinačnih antibiotika (INN) za terapiju vanbolničke pneumonije kod dece mlađe od 5 godina (A) i populacije dece starije od 5 godina i adolescenata (B)*

than to younger children (Odds Ratio (OR): 1.94, 95% Confidence Interval (CI): 1.13 – 3.33) [19].

Our results also showed off-label antibiotic prescribing for some indications not approved by the regulatory authority. These were doxycycline and ofloxacine which are contraindicated for children and adolescents. What is even more worrying is the fact that doxycycline (capsule) were prescribed to children younger than 12 months.

The national guidelines recommend amoxicillin and amoxicillin in combination with clavulanic acid as the first and second line therapy, respectively, to treat otitis media and mastoiditis. The guideline for otitis media recommends delayed prescribing of antibiotics and non-prescribing of these drugs in the first 2-3 days due to spontaneous remission of symptoms and healing in 70-90% of cases. Contrary to these recommendations, the second line therapy, amoxicillin in combination with clavulanic acid, was the most widely prescribed antibiotic in treatment of otitis media, which confirmed the non-compliance with the guidelines in region of Niš.

Recommendations about therapy of otitis media have undergone significant changes over the years. Antibiotics were the standard therapy of otitis media in the majority of developed countries at the end of XX century [20, 21]. However, later studies showed that spontaneous remission of symptoms and healing eventually occurred in a great number of patients. Moreover, early administration of antibiotics could result in the alleviation of symptoms after 24 hours (not immediately), but it could also increase the incidence of diarrhoea in children. Therefore, the strategy of delayed antibiotic prescribing has been recommended as the strategy of choice. This strategy could contribute to the reduction in antibiotic prescribing by even 76% [22]. The last Cochrane Review (2009) also prioritized antibiotic non-prescribing [23] because 16 children should be treated by an antibiotic in order to prevent one otitis media with pain symptoms. Thus, it is recommended to prescribe antibiotics only in children younger than 2 years of age having bilateral inflammation or inflammation of one ear and otorrhea [24]. Identical recommendations are observed in Great Britain [18] and the United States [25].

About 2% of children in region of Niš consumed one of the antibiotics every day in therapy of lower RTIs. Azithromycin and cefixime (3rd generation of cephalosporins) were the most widely prescribed antibiotics in treatment of lower RTIs throughout the observed period. According to our results, antibiotics prescribed for community-acquired pneumonia accounted for less than 10% in the total antibiotic prescribing for lower RTIs. Since antibiotics should not be prescribed to treat lower RTIs except for community-acquired pneumonia, it is obvious that these recommendations have not been adhered to.

In addition, the guidelines recommend amoxicillin as the first choice in treatment of community-acquired pneumonia in children under 5 years of age, except for infections caused by mycoplasmas, when macrolides are recommended as the first choice. Azithromycin and clarithromycin are recommended as the first choice in children older than 5 years of age, as well as in adolescents. According to our results, 2nd and 3rd generations of cephalosporins, recommended as the second line therapy, were the most widely prescribed in treatment of lower RTIs in region of Niš. Therefore, it could be concluded that doctors did not completely comply with the national recommendations in therapy of community-acquired pneumonia in children under 5 years of age. However, they completely observed the recommendations given in 2010 for treatment of community-acquired pneumonia in children older than 5 years, bearing in mind that the most widely prescribed antibiotics were azithromycin and clarithromycin.

According to the recommendation of the World Society for Pediatric Infectious Diseases based on high level of evidence, prescribing of antibiotics should be avoided in pre-school children in routine clinical practice because of infections caused by viruses in this age group. If it is necessary to prescribe antibiotic, amoxicillin is recommended as the first choice in all age groups of children and adolescents, while macrolides are recommended in case of infections caused by untypical pathogens [26]. Unfortunately, the consumption of amoxicillin in treatment of community-acquired pneumonia in children in region of Niš was extremely low, being only 0.001%.

The results of our research showed that the per cent of antibiotic prescribed in case of a diagnosis of upper RTI was five times higher than in case of a diagnosis of lower RTI. Similar results were reported in previous studies [12].

Foreign guidelines as well as clinical studies have recommended the strategy of delayed antibiotic prescribing as useful even in case of lower RTIs [18, 27]. It is also advisable to inform patients and parents about long persistence of symptoms of infection, particularly cough which could last for as long as 4 weeks. Cough could persist in spite of antibiotic administration due to moderate impact of antibiotics on the severity of symptoms but not on the persistence of symptoms.

Several authors analyzed reasons for prescribing antibiotics for children. One of the reasons is that the patients expect to be treated by antibiotics and the other one is that the doctors themselves think that antibiotics are necessary. In addition, several studies reported that doctors were under pressure exerted by patients and parents who wanted to get antibiotic prescription [28, 29]. However, other studies showed that 90% of the patients who had expected an antibiotic from the doctor were satisfied with the explanation that the delayed pre-

scribing or administration of antibiotic would be a better option [30, 31]. These results showed that clinical practice could be improved by decreasing antibiotic consumption in infections which are "traditionally" caused by viruses.

Dutch authors also analyzed the reasons why the doctors do not comply with the guidelines [32]. They found that the majority of them reported medical reasons, such as the severity of disease, comorbidities, as well as habits, calming the patient, the patient's request and others.

Our study has several limitations. In spite of the fact that RTIs are among the most frequent reasons for antibiotic prescribing in children, it could not generalize all bacterial infections. The unit DID, being a well-accepted statistical unit for drug consumption, was used as a measure of antibiotic consumption. However, a DDD was defined as the assumed average maintenance dose per day in adults, as it was earlier stated [16]. In the situation of high variability in drug dosing regimes in children, a DDD for adult was recommended to be used even in children. In addition, our analysis included only oral dosing forms, while intramuscular forms were not included so a higher antibiotic consumption in children in the observed period could be expected.

Conclusion

The total antibiotic consumption in children in region of Niš decreased during the observed period. However, the total antibiotic consumption in children was very high, particularly in case of upper respiratory tract infections. Antibiotic prescribing is not in accordance with the national guidelines either in case of upper respiratory tract infections or lower ones, which suggests irrational antibiotic consumption. Prescribing practice in region of Niš is in line with the national guidelines only in case of community-acquired pneumonia in children older than 5. It often happens that the diagnosis becomes an excuse for antibiotic prescribing instead of being the main reason.

Excessive antibiotic consumption leads to antibiotic resistance, which results in consumption of newer antibiotics of broader spectrum, and even higher health care expenses. The strategy of delayed antibiotic prescribing should become a part of routine clinical practice in region of Niš.

Irrational antibiotic prescribing could be decreased by continuous professional education of doctors and strict adherence to guidelines regarding antibiotic prescribing.

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Rad je primljen 23. VIII 2013.
Recenziran 5. III 2014.
Prihvaćen za štampu 23. VI 2014.
BIBLID.0025-8105:(2014):LXVII:9-10:282-289.

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