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Review

The profile of antibiotic prescriptions in pediatric outpatients: a retrospective observational study

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Background. Antimicrobial therapy is a common practice in pediatrics.

Aim. The main objective was to determine and characterize the profile of antibiotic prescriptions in pediatric outpatients.

Methods. This was a retrospective observational study performed in two pharmacies in Lviv (October 2021). 113 written doctor's prescriptions for outpatient children were collected.

Results. Antibiotics were administered for 44.2% (95%CI 34.9%–53.9%) of patients. The main reasons for antibiotic prescriptions were acute tonsillitis (30.0%) and acute upper respiratory tract infections (26.0%). Macrolides, cephalosporins, penicillins, and sulfonamides with trimethoprim presented 40.0%, 36.0%, 20.0%, and 4.0% of antibiotic prescriptions, respectively. Antimicrobials from the Access group accounted for 26.0% of antibiotic prescriptions (instead of at least 60.0%, WHO) and antibiotics from the Watch group constituted 74.0% (instead of a maximum of 40.0%, WHO). Antibiotics were prescribed to 61.9% of outpatients with acute upper respiratory tract infections, 93.7% of patients with acute tonsillitis, and 45.5% – with otitis media instead of recommended 0-20% (ESAC-Net). The first-line antibiotics were used in 23.1% of cases of acute upper respiratory infections, 26.7% of cases of acute tonsillitis, and 40.0% of otitis media, which is below the acceptable range (80–100%, ESAC-Net). In total, 22 antibiotic-associated drug-related problems (DRPs) were found in 34.0% of written doctor's prescriptions with antimicrobials. The most common were: (1) excessive length of therapy (36.4%) and (2) potential drug-drug interactions (31.8%).

Conclusions. The rate of antibiotic prescriptions for children is high and associated with different DRPs. The majority of antibiotic prescription quality indicators are outside the recommended ranges. Thus, effective interventions and campaigns to improve antibiotic therapy in children are needed.

Keywords: Anti-bacterial agents; pediatrics; outpatients; inappropriate prescribing; quality indicators.

Introduction

Antimicrobials for systemic use are among the most frequently administrated drug classes for children, especially preschool children [1-3]. Most antibiotics for pediatric patients (up to 90%) are prescribed in ambulatory care settings [4]. At the same time, antibiotic prescriptions for patients under 18 years of age present a serious clinical and socio-economic issue due to their irrational usage [4-6]. In some countries, up to 65% of antibiotic prescriptions are inappropriate and associated with numerous drug-related problems (DRPs) [6-7].

The overuse and misuse of antimicrobials in childhood can cause harmful outcomes, such as antimicrobial resistance, allergy, gastrointestinal disorders, overweight, and obesity [4,6,8-9]. Nowadays, various interventions are suggested to optimize the use of antibiotics: (1) minimization of antibiotic prescription; (2) decreasing the length of therapy; (3) prescription of antibiotics with the lower resistance potential according to the AWaRe classification, etc. [10-11]. Implementation of different approaches towards rational antibiotic use, for instance, in Germany and France, allowed these countries to decrease antibiotic prescription and, consequently, the risk of antibiotic-related problems [12-13]. According to scientific literature, good-quality antibiotic prescriptions for children in ambulatory care settings are keys to controlling antibiotic resistance [14].

Different metrics are used for antibiotic prescription improvement. For example, defined daily dose per 1000 inhabitants per day, days of antibiotic therapy per 1000 inhabitants/day, and so on [15]. For this reason, antibiotic therapy quality indicators for European outpatients have been developed [16].

There is limited data in Ukraine in this area. Thus, the present study aimed to analyze the profile of antibiotic prescriptions for outpatients under 18 years of age by evaluating (1) prescription rates and distribution of antibiotics by classes, (2) quality indicators of antibiotic prescriptions, (3) conformity to the AWaRe classification, and (4) rates and types of antibiotic-associated DRPs.

Materials and Methods

Definitions

AWaRe classification is a classification of antibiotics into three groups (Access, Watch, and Reserve), taking into account the impact of different antibiotics and antibiotic classes on antimicrobial resistance [17].

Quality indicator of antibiotic prescriptions is a measurable element of prescription performance, for which there is evidence or consensus that it can be used to assess the quality and, therefore, to change the quality of care provided. It is a percentage of patients who received the recommended drug treatment, with the numerator comprising the number of patients actually receiving the treatment and the denominator comprising the number of all patients for whom the treatment is appropriate [16].

A drug-related problem (DRP) is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes [18].

Written doctor's prescription is a paper prescription of drugs for outpatients but without the completion of a special form (receipt).

Data collection and analysis

The original data were collected in October 2021 in two pharmacies in Lviv. We obtained 113 written doctor's prescriptions for outpatients under 18 during the study period. Out of 113 doctor's prescriptions, 50 included antibiotics. The stages of the study are shown in Figure 1.

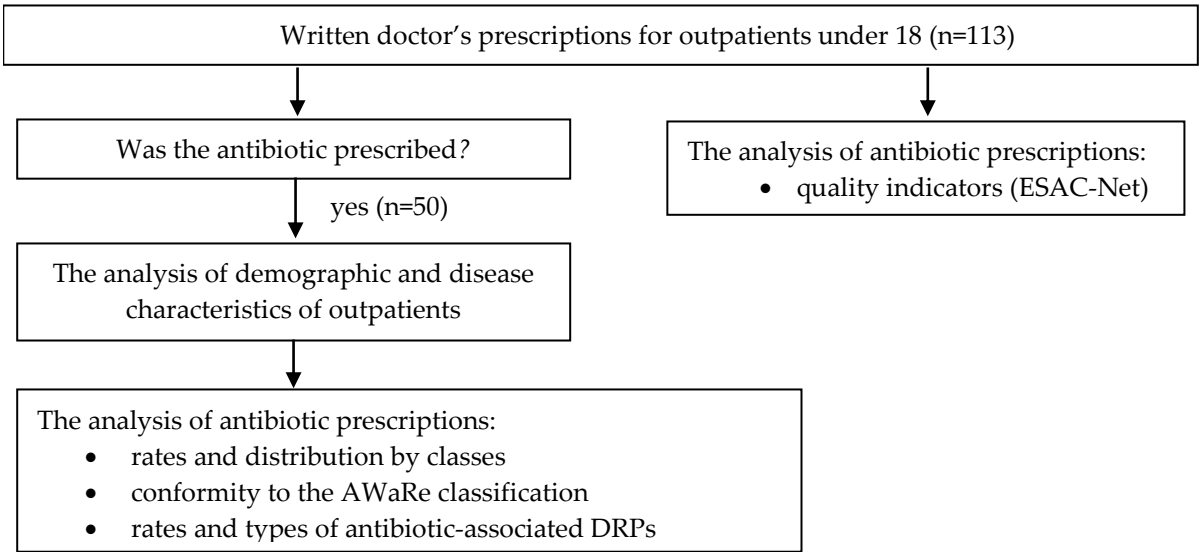

Figure 1. The flowchart of the study

Patients who were prescribed antibiotics were involved in the analysis of demographic and disease characteristics. Evaluating the appropriateness of antibiotic prescriptions was done in accordance with the AWaRe classification [17]. The identification of DRPs was carried out according to the Pharmaceutical Care Network Europe (PCNE) DRPs classification v5.01 [18]. The State Register of Medicinal Products of Ukraine [19] and Medscape [20] were used for pharmacotherapy assessment.

The antibiotic therapy quality indicators were calculated according to the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) proposed standards [16]. These standards include 21 quality indicators of antibiotic prescription for outpatients. Out of them, 9 quality indicators are applicable for the assessment of antibiotic therapy in children in cases of (1) acute upper respiratory tract infections, (2) acute tonsillitis, and (3) acute otitis media [16]. All collected doctor's prescriptions (n=113) were involved in this study stage.

Statistical analysis

Descriptive statistics were used to describe the characteristics of patients and antibiotic therapy. Qualitative variables were given as frequencies and percentages with a 95% confidence interval (CI). Quantitative variables (age, number of prescribed drugs, the length of antibiotic treatment) were checked for the type of distribution with the Shapiro–Wilk test and presented as medians with interquartile ranges (Q1–Q3) due to their non-normal distribution. The statistical analyses were performed with SPSS Trial.

Results

The rate of antibiotic prescriptions for outpatient children was 44.2% (95%CI 34.9%–53.9%). The distributions of demographic and clinical characteristics of the study population (n=50) are summarized in Table 1.

Table 1. The characteristics of outpatients (n=50) who were prescribed antibiotics

Characteristics	Frequency (%)	Median (Min–max)	Interquartile range (Q1–Q3)
Age, years		4.5 (0–14.0)	3.0 (3.0–6.0)
under 1	4 (8.0)		
1 to 3	6 (12.0)		
3 to 6	24 (48.0)		
6 to 12	13 (26.0)		
over 12	3 (6.0)		
Gender			
female	29 (58.0)		
male	21 (42.0)		
Diagnosis			
acute tonsillitis	15 (30.0)		
acute upper respiratory tract infections	13 (26.0)		
acute bronchitis	7 (14.0)		
acute otitis media	5 (10.0)		
acute sinusitis	4 (8.0)		
skin rash	2 (4.0)		
acute urinary tract infections	2 (4.0)		
others*	2 (4.0)		
Number of prescribed drugs		5.0 (2.0–10.0)	2.0 (4.0–6.0)
≤4	21 (42.0)		
5-7	27 (54.0)		
≥8	2 (4.0)		

*Diarrhea; Lyme borreliosis.

The median age of patients was 4.5 years. Most participants (58.0%) were females. The main reasons for taking antibiotics were acute tonsillitis (30.0%) and acute upper respiratory tract infections (26.0%). Macrolides, cephalosporins, penicillins, and sulphonamides with trimethoprim presented 40.0%, 36.0%, 20.0%, and 4.0% of antibiotic prescriptions, respectively (Table 2).

Table 2. Characteristics of antibiotic prescriptions (n=50)

Characteristics	Frequency	
	n	%
Macrolides	20	40.0
Azithromycin (n=18)		
Clarithromycin (n=1)		
Spiramycin (n=1)		
Cephalosporins	18	36.0
Cefpodoxime (n=8)		
Cefixime (n=6)		
Cefuroxime (n=3)		
Cephalexin (n=1)		
Penicillins	10	20.0
Amoxicillin + clavulanic acid (n=8)		
Amoxicillin (n=2)		
Sulfonamides and trimethoprim	2	4.0
Sulfamethoxazole + trimethoprim (n=2)		
Oral dosage forms		

suspensions	40	80.0
tablets	10	20.0
The length of antibiotic therapy, days		
<5	9	18.0
≥5	41	82.0
AWaRe* classification		
Access group	13	26.0
Watch group	37	74.0
Reserve group	0	0.0

*AWaRe classification: **A**ccess, antibiotics showing lower resistance potential; **Wa**tch, antibiotics at relatively high risk of bacterial resistance; **Re**serve, antibiotics that should be reserved for treatment of infections due to multidrug-resistant organisms [17].

The length of antibiotic treatment was 3 to 10 days (median 5.0; interquartile range 2.0; Q1=5.0; Q3=7.0). Most children (82.0%) received antibiotics for 5 days or more.

Antimicrobials of the Access group covered 26.0% (95%CI 14.6%–40.3%) of antibiotic consumption, Watch group – 74.0% (95%CI 59.7%–85.4%).

Calculated values of antibiotic quality indicators are presented in Table 3.

Table 3. Disease-specific quality indicators (ESAC-Net) of antibiotic therapy in outpatients

Variables	Acute upper respiratory tract infections	Acute tonsillitis	Acute otitis media
Outpatients over 1 year of age receiving antibiotics for systemic use, % (n)	61.9 (13/21)	93.7 (15/16)	45.5 (5/11)
95% CI	38.4–81.9	69.8–99.8	16.7–76.6
acceptable range* (%)	0–20	0–20	0–20
Outpatients over 1 year of age receiving recommended antibiotics (penicillins)**, % (n)	23.1 (3/13)	26.7 (4/15)	40.0 (2/5)
95% CI	5.0–53.8	7.8–55.1	5.3–85.3
acceptable range* (%)	80–100	80–100	80–100
Outpatients over 1 year of age receiving quinolones, %	0	0	0
95% CI	0	0	0
acceptable range* (%)	0–5	0–5	0–5

*According to the ESAC-Net recommendations. **Penicillins were considered as recommended first-choice antibiotics (taking into account ESAC-Net recommendations and Ukrainian guidelines for the management of acute upper respiratory infections [21], acute tonsillitis [22], and acute otitis media [23]).

Antibiotics were prescribed to 61.9% of outpatient children with acute upper respiratory infections, 93.7% with acute tonsillitis, and 45.5% with otitis media. Of these children, 23.1%, 26.7%, and 40,0% received recommended first-choice antibiotics for acute upper respiratory infections, acute tonsillitis, and otitis media, respectively. Quinolones were not prescribed at all.

Inappropriate prescription of different drug classes was identified in 40 (80.0%) participants among 50 and inappropriate prescription of antibiotics – in 17 (34.0%, 95%CI 21.2%–48.8%). The total number of DRPs was 78. Among them, 22 (28.2%) were related to antibiotics (Figure 2).

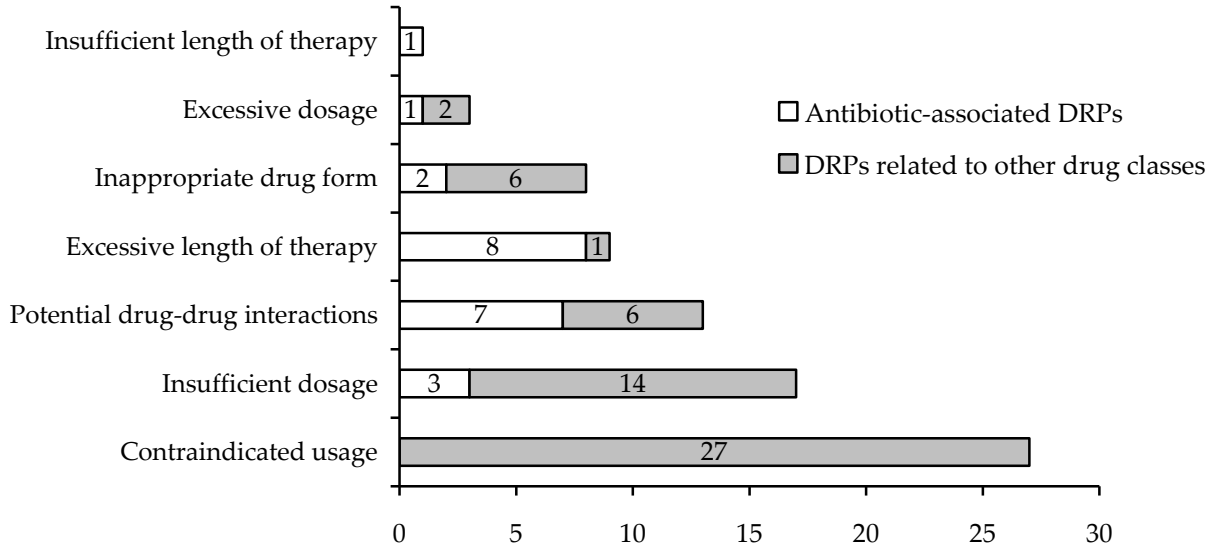

Figure 2. Distribution of DRPs (n=78)

In total, 6 antibiotic-associated DRPs were identified: (1) excessive length of therapy (36.4%); (2) potential drug-drug interactions (31.8%); (3) insufficient dosage (13.6%); (4) inappropriate drug form (9.1%); (5) excessive dosage (4.5%); (6) insufficient length of therapy (4.5%).

Discussion

The optimization of antibiotic prescription, including for pediatric patients, is among the main objectives of the global action plan on antimicrobial resistance [24]. Thus, we aimed to analyze the outpatient antibiotic profile in this age group, commonly exposed to antibiotics, and compare calculated values of different antibiotic prescription indicators to those recommended by ESAC-Net and AWaRe classification.

The prevalence of antibiotic prescriptions in pediatric outpatients differs significantly depending on age [1,5]. In our study, the rate of antibiotic prescriptions was the highest (48.0%) in outpatients aged 3 to 6 and the lowest (6.0%) in adolescents. This distribution confirms the results of numerous previous studies, that showed the predominance of antibiotic use in preschool children [4-5,9,25].

According to the scientific literature, the most common diagnoses for antibiotic prescription in childhood are acute otitis media, acute pharyngitis, and acute bronchitis [5,11]. Our findings disagree with these results because the most common reasons for antibiotic treatment were acute tonsillitis (30.0%) and acute upper respiratory infections (26.0%). Macrolides represented the most frequent antibiotics (40.0%), followed by cephalosporins (36.0%). The high rate of macrolides appears inappropriate. Neither Ukrainian nor international guidelines consider macrolides as first-line antibiotics [16,21-23]. Moreover, the overuse of macrolides is a clinical and socio-economic issue due to the high risk of bacterial resistance [17]. This fact, at least in part, explains the predominance of penicillins in the United States and some European countries (the Netherlands, Denmark, Italy, and Spain) [1,5,26-27]. In China, cephalosporins account for the majority of antibiotic prescriptions for this purpose [25,28].

According to the WHO recommendations, at least 60% of total antibiotic consumption should include antibiotics from the Access group and no more than 40% – from the Watch group (AWaRe classification) [17]. Nevertheless, in some countries, the Watch group constituted up to 74% of total antibiotic use in inpatient children [29] and up to 89% in outpatients [28]. We established that the percentage of the Watch group antibiotics was much higher than what WHO recommends (74.0% vs 40.0%). This result reveals that doctors often prescribe antibiotics with a higher potential of antimicrobial resistance instead of using antibiotics with lower risk.

The next step of this study was to calculate quality indicators of antibiotic prescriptions and compare the values with the approved recommendations (ESAC-Net). Our findings showed that 61.9% of outpatients with acute upper

respiratory infections, 93.7% – with acute tonsillitis, and 45.5% – with otitis media received antibiotics. These values are much higher than the approved ESAC-Net acceptable range (0–20%, ESAC-Net). First-line antibiotics (penicillins) were prescribed to 23.1% of patients with acute upper respiratory infections, 26.7% – with acute tonsillitis, and 40.0% – with otitis media, which is below the acceptable range (80-100%, ESAC-Net). At the same time, none of the participants took quinolones. The restricted prescription of quinolones agrees with the approved standards (0–5%, ESAC-Net). Thus, most antibiotic prescription indicators (6 of 9) were outside the recommended ranges with significant antibiotic overtreatment. Similar results have been found in England and Wales [14].

As described in the literature, antibiotic therapy in childhood is associated with numerous DRPs, and, consequently, with a high risk of adverse reactions, antibiotic resistance, and treatment failure [6-7]. In this study, 34.0% of written doctor's prescriptions included antibiotic-related DRPs. The most common subset of antibiotic-associated DRPs was an excessive length of therapy (36.4%), followed by potential drug-drug interactions (31.8%). Generally, azithromycin was involved in both of these subsets of DRPs. At the same time, (1) excessive dosage and (2) insufficient length of therapy were the least common DRPs related to antibiotics. Defined distribution does not go along with the results received in other studies, where inappropriate drug selection and wrong dosage were the most frequent DRPs [6-7].

The development and implementation of antimicrobial stewardship programs is a key to solving the problem of antibiotic overconsumption and inappropriate use [30]. These programs include many-sided interventions such as (1) promoting appropriate antibiotic use, (2) educating clinicians and patients, (3) monitoring antibiotic prescription data, etc. [31, 32]. Monitoring antimicrobial prescriptions for outpatients is essential and, simultaneously, one of the most challenging steps of antimicrobial stewardship programs. Scientific articles report that e-prescriptions are an accurate and effective tool for collecting and analyzing antibiotic prescription data [30-32]. Thus, the integration of e-prescriptions into the electronic health system of Ukraine will ensure the possibility of further studies related to the optimization of antibiotic use and will provide the development and implementation of national antimicrobial stewardship programs.

In conclusions: The rate of antibiotic prescriptions for outpatient children is high. Numerous DRPs are associated with antibiotic administration for patients under 18. Children aged 3 to 6 are more exposed to antibiotics, which are prescribed primarily due to acute tonsillitis and acute upper respiratory infections. The Watch group accounted for over 70% of antibiotic prescriptions, with macrolides and cephalosporins predominance. The majority of quality indicators of antibiotic prescriptions were outside the recommended ranges. Thus, the current profile of antibiotic prescriptions in pediatric outpatients shows the need for different interventions and campaigns to improve antibiotic prescription in this target group and highlights the scope for further studies.

Study limitations. This study has several limitations. First, we assume some inaccuracy in the distribution of diagnoses due to the absence of diagnosis codes on written doctor's prescriptions according to international recommendations. Second, this was a retrospective study based only on information from the written doctor's prescriptions. Thus, the number of DRPs is plausibly more than we calculated. In addition, we collected the original data only in two pharmacies. This fact limits the generalizability of our results.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the bioethics committee of Danylo Halytsky Lviv National Medical University, protocol No. 10 of 16.12.2019.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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