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Trends of antibiotic consumption in pediatric inpatients, a retrospective study in Lviv, Ukraine

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ABSTRACT

The objective of this study was to assess the consumption of antibiotics in children using the «AWaRe» classification of antibiotics (WHO, 2017) and metrics such as days of therapy (DoT) and length of therapy (LoT) per 1000 patient-days (PD). Antibiotics were administrated to 91.1% of inpatients in 2019 and 68.2% in 2021 ($p<0.05$). The main reason for antibiotic prescription was acute bronchitis in both study periods. Total DoT/1000 PD increased from 717.0 in 2019 to 760.0 in 2021 ($p<0.05$), and total LoT/1000 PD from 679.0 to 717.4 ($p<0.05$). Administration of antibiotics from the Access group decreased from 2.1% in 2019 to 1.8% in 2021 ($p>0.05$), antibiotics from the Watch group increased from 90.7% to 97.3% ($p>0.05$). Although a statistically significant reduction in the antimicrobial prescription rate, we found a considerable increase in (1) prescription antibiotics with a high risk of antimicrobial resistance, and (2) the main units of antimicrobial consumption.

Keywords: antibiotics, antimicrobial consumption, hospitals, children, inpatients

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INTRODUCTION

Nowadays, antibiotics are one of the most prescribed medicines in the pediatric population, especially in hospital wards[1,2,3]. The prevalence of antibiotic prescription in hospitalized children varies significantly in different countries, with the worldwide average at 37%[4]. Simultaneously, a high rate of antimicrobial administrations is unnecessary or incorrect, accounting for up to 50% of total antibiotic prescriptions[5].

This group of medicines is responsible for numerous adverse reactions, notably gastrointestinal and hematological disorders[6]. Furthermore, inappropriate use and overconsumption of antibiotics significantly increase the risk of drug-resistant pathogen occurrence and spreading[7]. According to the World Health Organization (WHO) reports, antimicrobial resistance is one of ten global public health threats associated with a high rate of morbidity and mortality[8]. About 1.3 million deaths per year worldwide are directly related to drug-resistant bacteria defining antimicrobial resistance as a frequent cause of fatalities[9].

Davey P. et al. found that reducing antibiotic use in hospitals decreases the risk of antimicrobial resistance[7]. Different metrics evaluate the antimicrobial prescribing trends in hospitals[10]. For instance, the defined daily dose (DDD) is a technical unit of antimicrobial consumption in hospitalized adults. Although this is the most commonly used unit, it has some limitations for pediatrics[11]. Thus, alternative metrics, such as (1) days of therapy (DoT) and (2) the length of therapy (LoT), describe the quantification of antimicrobial utilization in children[4,11]. Also, the AWaRe classification lets practitioners reduce the use of antibiotics with a high potential for antimicrobial resistance[12]. Overall, the analysis of antibiotic consumption in inpatient children is essential. Not only does it optimize antibiotic treatment, but also it helps to implement different interventions of antimicrobial policy[7,11]. Numerous studies in Canada[13], Spain[14], and Germany[15-17] report that the calculation of the abovementioned metrics evaluates the effectiveness of antibiotic stewardship programs.

Though overconsumption and inappropriate use of antibiotics in pediatrics are not new issues, there is little available information about this problem in Ukraine. With this background, we aimed to (1) define the trends of antimicrobial consumption in hospitalized children, (2) identify the problem areas of antibiotic prescription and (3) highlight the necessity of antimicrobial stewardship programs development and implementation in Ukraine.

METHODOLOGY

Definitions

AWaRe classification – a grading of antibiotics into three groups (Access, Watch, and Reserve), developed by WHO to support antibiotic stewardship efforts. The background of this classification is the impact of different antibiotics and antibiotic classes on antimicrobial resistance[12].

Days of therapy (DoT) – the number of days a patient receives an antimicrobial agent irrespective of single and daily doses. All doses of one antibiotic received throughout a day are 1 DoT. If patients received more than one antibiotic, we calculated DoT for each antimicrobial agent[17,18].

Length of therapy (LoT) – the number of days a patient receives antimicrobials (one or more)[17,18].

Data collection and analysis

This retrospective study was conducted in the Pediatric Unit in one of Lviv city hospitals. This Unit admits children aged 1 to 18 years due to different somatic diseases (with respiratory system disorders prevalence). We acquired copies of medical records (123 in March 2019 and 129 in March 2021) with an agreement with the hospital administration. The reason for choosing March was that it is a time of the year with a steady medium number of inpatients in this Unit. Information regarding demographic (age, gender) and clinical (diagnosis, comorbidity, allergy, administration of antibiotics) characteristics we extracted from the medical records. Antibiotic consumption was assessed using the AwaRe classification12 and units such as DoT and LoT[4,11,15,17]. These units were standardized per 1000 patient days (PD) (taking into account the length of stay of each patient) and compared in 2 study periods (2019 and 2021).

Limitations

Necessary information we obtained retrospectively from paper medical records. The analysis of this type of documentation requires a lot of time and human resources. Thus, medical records of patients admitted to the hospital in 1 month (from 1 to 31 March 2019 and 2021) were enrolled. Consequently, we did not calculate the annual total antibiotics consumption but managed to evaluate its tendency. The quantification of antimicrobial utilization measured as DoT and LoT per 1000 PD did not include doses and frequency regimen of antibiotic treatment, which is another disadvantage of this study. Carrying out the research only in Pediatric Unit and only in one hospital restricts the generalizability of our findings. Further studies are needed to evaluate antimicrobial consumption in other wards and hospitals.

Statistical analysis

The statistical analysis was performed with SPSS Trial. Qualitative variables were summarized as frequency (n) and percentage (%), while quantitative variables were described as mean with standard deviations (SD). To test the difference between the two study periods (2019 and 2021), the Mann–Whitney U test was used for quantitative variables and Chi-square or Fisher's tests for qualitative variables14. The value of $p<0.05$ was statistically significant. This research received ethical approval from the Human Research Ethics Committee of Danylo Halytsky Lviv National Medical University in December 2019 (Protocol No. 10).

RESULTS and DISCUSSION

Overall, 252 pediatric inpatients were included in the study sample (123 in 2019 and 129 in 2021). Among them, 91.1% in 2019 and 68.2% in 2021 received at least one antibiotic ($p<0.05$). The main characteristics of hospitalized children distributed by study periods are presented in Table 1.

Table 1. Main characteristics of inpatient children who received antibiotics

Characteristics	2019		2021		p
	n	%	n	%	
Number of patients	112		88		
Gender male female	 53 59	 47.3 52.7	 39 49	 44.3 55.7	0.672
Age (min-max) from 1 to 5 years from 5 to 12 years from 12 to 18 years	1-16 64 40 8	 57.1 35.7 7.2	1-17 56 27 5	 63.6 30.7 5.7	
Mean age ± SD, years	5.5 ± 3.7		5.1 ± 3.8		0.348
Allergy yes no	 4 108	 3.6 96.4	 3 85	 3.4 96.6	0.951
Co-morbidity yes no	 15 97	 13.4 86.6	 18 70	 20.5 79.5	0.182
Diagnosis acute bronchitis community-acquired pneumonia others*	 72 39 1	 64.3 34.8 0.9	 62 14 12	 70.5 15.9 13.6	0.357 0.003

*Others in 2019: acute pyelonephritis (n=1); others in 2021: acute laryngotracheitis (n=4), acute obstructive laryngitis (n=2), acute nasopharyngitis (n=1), chronic sinusitis (n=1), acute pansinusitis (n=1), asthma (n=1), systemic inflammatory response syndrome of infectious origin (after COVID-19) without organ failure (n=1), functional disorder of stomach (n=1)

There were no statistically significant differences ($p>0.05$) in gender, age, allergy, and co-morbidity in 2019 and 2021. The main reason for antibiotic administration in both study periods was acute bronchitis (64.3% vs 70.5% in 2019 and 2021, respectively, $p>0.05$), followed by community-acquired pneumonia, the rate of which decreased significantly from 34.8% in 2019 to 15.9% in 2021 ($p<0.05$).

The total number of prescribed antibiotics was 139 in 2019 and 107 in 2021 (mean 1.2 ± 0.5 vs 1.2 ± 0.4, respectively, $p=0.826$; minimum one antibiotic, maximum three antibiotics in both periods).

According to the «AWaRe» classification, 90.7% of antimicrobials in the first period of study and 97.3% in the second period of study were from the Watch group ($p>0.05$). Ceftriaxone (43.2% and 29.0% in 2019 and 2021, respectively, $p<0.05$), azithromycin (18.0% and 18.7%, $p>0.05$), cefotaxime (9.4% and 40.2%, $p<0.05$) and cefoperazone (9.4% and 3.8%, $p>0.05$) presented the most common antibiotics from Watch group. The rate of antimicrobials from the Access group was 2.1% and 1.8% in the first and second periods of the study, respectively ($p>0.05$). This group involved amikacin (1.4% and 0.9% in 2019 and 2021), furazidin (0.7% in 2019) and sulfamethoxazole + trimethoprim (0.9% in 2021). The Reserve group (imipenem + cilastatin) was administrated only in 2019. The prevalence of this group accounted for 0.7% of the total antibiotics prescribed. Moreover, 6.5% of antimicrobials in 2019, and 0.9% in 2021 ($p<0.05$) were classified by AWaRe classification as not recommended. In 2019, this category included cefoperazone + sulbactam (5.8%) and ceftriaxone + sulbactam (0.7%), in 2021 – cefoperazone + sulbactam (0.9%).

The total number of PD in the first period was 1000, and in the second period – 700 (Table 2). Total DoT decreased from 717 to 532 days and total LoT from 679 to 503 days. However, standardized DoT per 1000 PD increased from 717.0 to 760.0 (+6%) with an average 5.2 ± 1.6 and 7.1 ± 2.3 in 2019 and 2021, respectively ($p<0.05$). Simultaneously, standardized LoT per 1000 PD rose from 679.0 to 717.4 with an average from 6.1 ± 1.9 to 8.2 ± 2.7 in 2019 and 2021, respectively ($p<0.05$).

Table 2. Summary of the antibiotic consumption data in 2019 and 2021

Antibiotic consumption data	2019	2021	p
Patient days (PD)	1000	700	
Days of therapy (DoT)			
Total DoT	717	532	
Total DoT/1000 PD	717.0	760.0	
Mean DoT/1000 PD ± SD	5.2 ± 1.6	7.1 ± 2.3	<0.05
Length of therapy (LoT)			
Total LoT	679	503	
Total LoT/1000 PD	679.0	717.4	
Mean LoT/1000 PD ± SD	6.1 ± 1.9	8.2 ± 2.7	<0.05

SD – standard deviation

There was a predominance of third-generation cephalosporins consumption (measured as DOT) in both study periods. These antibiotics accounted for 70.7% and 76.3% of total DoT in 2019 and 2021, respectively (Table 3). The highest rate of DoT in 2019 accounted for ceftriaxone (42.0%), and in 2021 - for cefotaxime (35.9%). Also, the consumption of macrolides was relatively high (17.7% of total DOT in 2019 and 18.4% in 2021).

Table 3. Comparison of detailed antibiotic consumption in 2019 and 2021

Antibiotics	2019			2021			Difference	
	Total DoT	DoT / 1000 PD	%	Total DoT	DoT / 1000 PD	%	DoT / 1000 PD	%
Third-generation cephalosporins	**507**	**507.0**	**70.7**	**406**	**580.0**	**76.3**	**73**	**14.4**
Ceftriaxone	301	301.0	42.0	182	260.0	34.2	-41	-13.6
Ceftriaxone, combinations	5	5.0	0.7	0	0	0	-5	-100.0
Cefoperazone	66	66.0	9.2	20	28.6	3.8	-37.4	-56.7
Cefoperazone + sulbactam	45	45.0	6.3	7	10.0	1.3	-35	-77.8
Cefotaxime	71	71.0	9.9	191	272.9	35.9	201.9	284.4
Cefpodoxime	19	19.0	2.6	4	5.7	0.8	-13.3	-70.0
Cefixime	0	0	0	2	2.9	0.4	2.9	-
Macrolides	**127**	**127.0**	**17.7**	**98**	**140.0**	**18.4**	**13.0**	**10.5**
Azithromycin	127	127.0	17.7	91	130.0	17.1	3.0	2.4
Clarithromycin	0	0	0	7	10.0	1.3	10.0	-
Fluoroquinolones	**38**	**38.0**	**5.3**	**0**	**0**	**0**	**-38.0**	**-100.0**
Ciprofloxacin	24	24.0	3.3	0	0	0	-24.0	-100.0
Levofloxacin	14	14.0	2.0	0	0	0	-14.0	-100.0
Fourth-generation cephalosporins	**17**	**17.0**	**2.4**	**13**	**18.6**	**2.4**	**1.6**	**9.4**
Cefepime	17	17.0	2.4	13	18.6	2.4	1.6	9.4
Carbapenems	**11**	**11.0**	**1.5**	**5**	**7.1**	**0.9**	**-3.9**	**-35.5**
Meropenem	0	0	0	5	7.1	0.9	7.1	-
Imipenem/ cilastatin	11	11.0	1.5	0	0	0	-11	-100.0
Aminoglycosides	**9**	**9.0**	**1.3**	**3**	**4.3**	**0.6**	**-4.7**	**-52.2**
Amikacin	9	9.0	1.3	3	4.3	0.6	-4.7	-52.2
Second-generation cephalosporins	**5**	**5.0**	**0.7**	**0**	**0**	**0**	**-5.0**	**-100.0**
Cefuroxime	5	5.0	0.7	0	0	0	-5.0	-100.0
Nitrofurans	**3**	**3.0**	**0.4**	**0**	**0**	**0**	**-3.0**	**-100.0**
Furazidin	3	3.0	0.4	0	0	0	-3.0	-100.0
Sulfonamides	**0**	**0**	**0**	**7**	**10.0**	**1.3**	**10.0**	**-**
Sulfamethoxazole + trimethoprim	0	0	0	7	10.0	1.3	10.0	-
Total	**717**	**717.0**	**100.0**	**532**	**760.0**	**100.0**	**43.0**	**6.0**

As far as we know, this was the first study in Ukraine that described and evaluated the trends of antimicrobial consumption in hospitalized children. Overall, the frequency of antimicrobial treatment of hospitalized patients under 18 years differs worldwide, with the prevalence from 25% to 94% of inpatients in some European[19] and African[1] countries, respectively. This variety could be related to different factors, for instance, (1) the occurrence of infectious diseases[20], (2) the level of income in the county, and, consequently, the ability to perform the precise laboratory testing of the infection's origin, (3) medical staff experience and their attitude towards the antimicrobial resistance[19], (4) insufficient state regulation of antibiotic administration[20, 21], etc. Also, the rate of antimicrobial prescription depends on the type of hospital setting[22]. The pediatric intensive care units, neonatal units[22], and pediatric medical wards[22,23] are the settings with the highest level of antibiotic consumption. According to our results, the rate of antibiotic administration for inpatient children was high in both study periods and surpassed the pooled worldwide prevalence (37%)[4]. At the same time, the percentage of inpatients who received antibiotics decreased significantly from 91.1% in 2019 to 68.2% in 2021 ($p<0.05$), which could be related to different efforts directed to reduce antimicrobial utilization in Ukraine[24].

Children aged 1 to 5 years were most vulnerable to antibiotic prescriptions, similar to other studies[22,23,25]. In our case, females received antibiotics more often, which is content with results from Lithuania[22] and differs from findings in the United States[25], Latvia[22], and some other countries[20,23] with male predominance.

Scientific literature reports that respiratory tract infections are one of the main reasons for antibiotics prescription[19,22,23,26,27]. Our findings match this information because acute bronchitis was the most common diagnosis in both study periods. At the same time, it is known that upper respiratory tract infections are usually viral (for instance, up to 95% of acute bronchitis cases), with limited evidence-based data about the beneficial effects of antibiotics[28]. However, we cannot affirm the excessive use of antibiotics in this study due to its retrospective design.

We found third-generation cephalosporins (mainly ceftriaxone in 2019 and cefotaxime in 2021) the most common antibiotics. Also, the rate of macrolides (mainly azithromycin) was high. This result is similar to findings in numerous recent studies[22,23,29]. These cephalosporins and macrolides present the Watch group of antibiotics, the total rate of which increased from 90.7% to 97.3% ($p>0.05$). This tendency reflects the permanent problem of overusing broad-spectrum antibiotics with a high risk of resistance. According to the WHO recommendations[12], antibiotics from the Watch group should not exceed 40% of total antimicrobial consumption. Not only in Ukraine but also in other countries, such as Canada[30], China[26], Pakistan[27], and others[20,31], antibiotics with a high risk of resistance prevail. At the same time, the Access group presented about 2% of the total number of antibiotics in both study periods instead of recommended at least 60%[12]. This distribution indicates the inappropriateness of antibiotic use and the needfulness of antibiotic stewardship programs for inpatient children.

The global overuse of antibiotics, especially in hospitalized adults and children, defined the necessity of different metrics for evaluating antibiotic consumption[16,17]. Numerous units, such as (1) DDD, (2) DoT, (3) LoT per 1000 PD, and some others, describe antibiotic utilization in patients[10,20]. However, DoT and LoT are more applicable for pediatrics[16,17]. According to recent studies, in general pediatric wards, total antibiotic consumption varies from 392[16] to 483 DoT per 1000 PD[17]. In this study, the overall antibiotic utilization was much higher in both study periods (717.0 versus 760.0 DoT per 1000 PD, mean 5.2 ± 1.6 versus 7.1 ± 2.3 DoT per 1000 PD in 2019 and 2021, respectively, $p<0.05$). Moreover, our results demonstrate the same changes in LOT per 1000 PD (679.0 versus 717.4 LoT per 1000 PD, mean 6.1 ± 1.9 versus 8.2 ± 2.7 LoT per 1000 PD days in 2019 and 2021, respectively, $p<0.05$). Compared with other studies, the overall antibiotic LoT per 1000 PD was considerably higher than published data in general pediatric wards (no more than 377 LoT per 1000 PD)[17] and similar to pediatric intensive care units with 667 to 750 LoT per 1000 PD[15]. Thus, we found the deterioration of metrics that describe antibiotic consumption in hospitalized children. Many published reports show the efficacy of antibiotic stewardship programs in providing optimization of antimicrobial utilization[1,13,15-17]. These findings define further steps in this area in Ukraine.

Detailed analysis of antibiotic utilization revealed that third-generation cephalosporins accounted for 70.7% in 2019 and 76.3% in 2021 of total DoT per 1000 PD. The consumption of ceftriaxone, the most commonly used antibiotic in 2019, reduced by 41 DoT/1000 PD (-13.6%) in 2021. At the same time, the consumption of cefotaxime increased by 201.9 DoT/1000 PD (+284.4%), which was the most used antibiotic in 2021. These results differ from other studies, where penicillins and second-generation cephalosporins prevailed[16,17]. Moreover, scientific literature indicates a decrease in cephalosporins administration and an increase in penicillin consumption[16,17]. Notably, the reduction of third-generation cephalosporins (most common in intensive care units[15,16]) prescription ensures decreasing the risk of antimicrobial resistance and numerous other conditions, such as *Clostridium difficile* infections[32], immune hemolytic anemia[33], etc.

The consumption of macrolides was relatively high (17.7% and 18.4% of total DoT per 1000 PD in 2019 and 2021, respectively), with an increase of 13 DOT/1000 PD (+10.5%) in 2021. This result is much higher than in other studies (1.8-6.9%)[16]. In 2019 macrolides were followed by fluoroquinolones, usually associated with multiple adverse drug reactions in children[34]. However, in 2021 we found no one case of fluoroquinolones administration (-100.0%), which is a positive change in pediatrics[32].

Antibiotics are common medicines in pediatric inpatients. The rate of antibiotic prescriptions is high. However, a statistically significant reduction in patient rates received antimicrobials was found. Although this positive change, we established a statistically significant increase in main metrics of antimicrobial consumption such as (1) days of therapy and (2) length of therapy per 1000 patient days. Also, we found the deterioration of a permanent problem associated with the prescription of antibiotics with a high risk of resistance. Thus, there is a necessity for effective interventions to improve antibiotic therapy in hospitalized children in Ukraine.

STATEMENT OF ETHICS

The study received ethical approval from the Human Research Ethics Committee of Danylo Halytsky Lviv National Medical University (Protocol No.10 of 16.12.2019).

CONFLICT OF INTEREST STATEMENT

The authors report no conflict of interest.

AUTHOR CONTRIBUTIONS

Concept – Horodnycha O, Zimenkovsky A, Ryvak T (authors contributed equally); Design – Horodnycha O, Zimenkovsky A, Ryvak T (authors contributed equally); Data Collection and Processing – Horodnycha O; Statistical Analysis and Interpretation – Horodnycha O; Literature Search – Horodnycha O, Ryvak T; Drafting of the Manuscript – Horodnycha O, Ryvak T; Critical Revision of the Manuscript – Zimenkovsky A.

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