

DR ELIF OĞUZ (Orcid ID : 0000-0002-8052-671X)

DR BERNA TERZIOĞLU BEBITOĞLU (Orcid ID : 0000-0003-4601-7871)

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Evaluation of antibiotic use among hospitalized patients in a pediatric department of a training hospital in Turkey

Running Head: Antibiotic use in pediatric patients

Elif Oğuz¹, Berna Terzioğlu Bebitoğlu¹, Çağatay Nuhoğlu², Yasemin Çağ³, Ajla Hodzic¹, Fatime Temel¹, Pelin Çırtlık², Ayşe Ela Kurtan Dalkılıç²

¹ Department of Medical Pharmacology, Faculty of Medicine, Istanbul Medeniyet University, Istanbul, Turkey

²Department of Pediatrics, Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey

³Department of Infectious Diseases, Faculty of Medicine, Istanbul Medeniyet University, Istanbul, Turkey

Corresponding author: Elif Oğuz, Assoc Professor. Department of Medical Pharmacology, Faculty of Medicine, Istanbul Medeniyet University, Istanbul, Turkey

Email: eoguz73@yahoo.com; elif.oguz@medeniyet.edu.tr

Tel: +905074428544

Istanbul Medeniyet University, Medical Faculty

Ünalan Mahallesi, Ünalan Sok., D-100 Karayolu Yanyol, 34700 Üsküdar/Istanbul

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Keywords: Antibiotics, pediatric, prescription.

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ABSTRACT

Background: Antibiotics are widely used and inaccurate or inappropriate prescription of antibiotics causes a significant increase in the prevalence of multidrug-resistant bacterial infections among children. This research aimed to study antibiotic prescriptions in hospitalized pediatric patients and to determine the prevalence of inappropriate antimicrobial use and the main types of prescribing errors.

Methods: After obtaining the Ethics Committee approval, screening was conducted among 535 patients admitted to the Department of Pediatrics at Haydarpasa Numune Training and Research Hospital in the period of 01.01.2016 – 31.12.2016 who had been treated with an antibiotic. Patients' demographics, diagnosis, and antibiotic therapy details were collected using a standardized case report form and assessed by a clinical pharmacologist and an infectious disease specialist regarding the convenience and accurateness of antibiotic prescribing.

Results: Out of 535 antibiotic prescriptions, single antibiotics were used inappropriately in 216 (56.10%) of the patients and there were 39 (26%) unnecessary antibiotic combinations. Most of the errors were made in the dose frequency (55.69%), followed by indication (25.88%), administration route (16.08%), and dosage (2.67%).

Conclusions: The results of our study show that a high level of antibiotics in the pediatric clinic was misprescribed. Inappropriate usage increases the chances of microbial resistance and the cost of treatment. Precautions should be taken in this regard.

Keywords: Antibiotics; pediatric; prescribing error; microbial resistance.

WHAT'S KNOWN? (what is already known about this subject?)

Inappropriate use of antibiotics causes antimicrobial resistance and as the antibiotics become less effective, the treatment of common infectious diseases is becoming harder, sometimes impossible. Additionally, according to the data of the World Health Organization, Turkey has a high antibiotic use profile.

WHAT'S NEW? (what does this study contribute to the literature?)

Although the studies evaluating antibiotic prescribing in adults are common, studies on the use of antibiotics in children are limited. There is a need to determine the current situation of antibiotic use in pediatric patients in Turkey and also in other countries. The data of this study is important because it provides insights into the current practice of antibiotic prescribing, actual inappropriate antibiotic usage, and the most common errors made in pediatric patients.

Background

Today, antibiotics are the most prescribed drugs to children in hospital and community settings. Hospitalized pediatric patients have usually been treated with antibiotics during their hospitalization and it has been reported that many of these prescriptions were inappropriate (1,2). Unnecessary antibiotic use is frequently encountered in viral or non-infectious diseases. Antibiotics are prescribed mostly for respiratory tract infections whereas respiratory infections are frequently caused by a virus (3,4). Additionally, broad spectrum antibiotics are given to children who suffer from infections although narrow-spectrum antibiotics are sufficient and recommended for treatment (5). Inappropriate use of antibiotics is directly related to the increase of multidrug-resistant bacterial infections. According to the annual report 2017 of Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR), multidrug resistance was 18% in *E. Coli*, 35% in *K. Pneumoniae*, 28% in *P. aeruginosa*, and 76% in *Acinetobacter* spp. in Turkey in 2016. Twenty-three percent of *S. aureus* were methicillin-resistant *Staphylococcus aureus*

(MRSA). Multidrug resistance was 30% in *S. pneumoniae*. One per cent of *E. faecalis* isolates were resistant to vancomycin. In *E. faecium*, vancomycin resistance was 15% (6).

The data of a study conducted in Turkey related to national antimicrobial resistance surveillance system showed that antibiotic resistance is higher in our country in most cases among the countries in close geographical region and also there is an increase in resistance in time (7).

It was revealed that the growing resistance to antibiotics is a major problem for also pediatric patients in both Turkey (8) and other countries (9,10).

Besides the resistance problem, inappropriate antibiotic use also may lead to harmful adverse reactions among children. Children are certainly not small adults and these and many other differences must be considered during antibiotic prescribing. Age-related changes in pharmacokinetics and pharmacodynamics, different adverse drug reactions, pathophysiology, and variants of diseases are some of the differences in the use of antibiotics among pediatric patients compared to adult patients (11). Many prescribed antibiotics have incorrect dosage, inappropriate dose intervals, or are used longer than needed (2).

Investigation of antibiotic prescribing in pediatric hospitals is important for the determination of the current situation and for designing further plans for changing the inappropriate patterns of antibiotic prescribing (12). Although the studies evaluating antibiotic prescribing in adults are common, considering the current situation of antibiotic resistance the studies conducted in pediatric patients in Turkey and also in other countries remain insufficient.

This study will give information on current practice on antibiotic prescribing, actual inappropriate antibiotic usage, and the most common errors in pediatric patients.

Methods

Study design

We performed a single-centered, retrospective cohort study among hospitalized pediatric patients in Haydarpaşa Numune Training and Research Hospital between January 2016 and December

2016. Patients' demographics, diagnosis, and antibiotic therapy details were collected from the hospital database. Consultation with the prescriber was made if needed.

The study was approved by the Ethics Committee of Haydarpaşa Numune Training and Research Hospital (Approval number: HNEAH-KAEK 2017/54).

Study setting, population, and data collection

The screening was conducted among a total of 1500 (93.75%) patients admitted to the pediatric clinic of the hospital during this period and 565 of them had used antibiotics. We included 535 of these 565 patients with antibiotic use because of incomplete data for 30 of them. So we included 94.6% of pediatric patients who used antibiotics in the mentioned period. No control groups were included in this study.

The pediatric clinic included in this study has only a first level Neonatal Intensive Care Unit with 4 incubators, there is no pediatric intensive care department or division. One general ward with 21 and one Infectious Diseases ward with 15 beds is present. Also, there is a "General Rational Antibiotic Usage Committee" in this hospital, but there is no pediatric infectious disease specialist in the pediatric department. Some of the precautions made by this committee are: To start an antibiotic only if necessary, to use of a narrow-spectrum antibiotic if it is possible, to use broad-spectrum only when needed and an antibiogram -application.

The data were collected using a standardized case report form. The form included detailed information: patient demographics, duration of hospitalization, the etiology of the disease, preliminary and definitive diagnoses, physical and radiologic examination findings, diagnostic laboratory results, concurrent diseases and medications, smear findings (if present), infection origin, nutrition type, presence of liver or renal failure, name of the medication, dosage (amount of drug given at once), dose frequency (how many times a drug is given per day), dosage form, route of administration and duration) and if any, history of antimicrobial allergy or intolerance and therapy modifications for single or combination antibiotic usage.

The forms were assessed by a clinical pharmacologist and an infectious disease specialist regarding the accurateness of antibiotic prescribing (13,14).

Inappropriate use of antimicrobial agents prescribing was defined as having an error in one of the following: drug indication such as etiology of the disease, dosage, dose frequency, route of administration.

Statistical analysis

The SPSS statistical software (Version 22; SPSS Inc. Chicago, IL, USA) was used for data analysis. Descriptive statistics (frequency and percentage) were used to examine the data on antibiotic use such as appropriateness of the indication, dosage, dose frequency, and the route of administration.

The chi-square test was used to identify differences between the frequencies of used antibiotics among age groups. P values below 0.05 were considered significant.

Results

Total of 565 pediatric patients were found to have been treated with antibiotics in the selected period and 535 of these pediatric antibiotics used patients (94.6%) were included in the study. Among these, 25.63% of patients were prescribed antibiotics for home use at the discharge. The mean duration of hospital stay was 6.1 days. The minimum stay was 1 day and a maximum period of stay was 35 days.

The highest rate of antibiotic prescribing among 535 hospitalized pediatric patients was in children aged between 4 weeks to 1 year (41.12%) while the lowest one in the age group up to 4 weeks (4.3%). The most frequent diagnosis was related to pulmonary diseases (49.35%), followed by gastrointestinal (13.64%) and urinary system diseases (12.71%), (Table 1).

In this study, the most prescribed antibiotics were cephalosporins (45.24%), penicillins (28.28%), and macrolides (9.0%) (Table 2). There was statistically significant higher usage of penicillins, cephalosporins, glycopeptides, and aminoglycosides in the 4 weeks-1 year age group compared to the other age groups ($p < 0.05$) (Table 3).

Culture test was performed only in 15.8% of cases of the antibiotic-treated patients and out of all of the performed culture tests, only 8.03% were positive. All the other patients received antibiotics empirically.

In all of the prescriptions, 385 (71.96%) included single and 150 (28.04%) antibiotic combinations. The single antibiotics were used inappropriately in 216 (56.10%) of the patients and there were 39 (26%) unnecessary combinations.

Most of the errors were made in the dose frequency; where (55.69%) of drugs were prescribed less frequently than needed, indication (25.88%), administration route (16.08%), and dosage (2.67%). Indication errors were the most common error type in glycopeptides, macrolides, and aminoglycosides, dose frequency errors in penicillins, and administration route errors in cephalosporins. Additionally, the rate of errors in the indication and administration route was equal and higher than the other error types in nitroimidazoles and carbapenems. It was seen that the prescribing errors, in general, were most frequent in penicillins (58.24%), glycopeptides (25.92%), and aminoglycosides (20%) (Table 4).

According to the records, it was observed that there were no serious side effects associated with the use of antibiotics. None of the patients had liver or renal failure according to biochemical findings recorded by physicians.

Discussion

In this study, we determined the accurateness of antibiotic prescribing by reporting the errors in indication, dosage, dose frequency, and administration route where 56.10% of single and 26% of antibiotic combinations were considered inappropriate.

The most frequent diagnosis in this study were pulmonary diseases (49.35%) followed by gastrointestinal diseases (13.64%) and urinary system diseases (12.71%). Similar results were seen in the studies of Bhupalam et al. (15) and Sharma et al. (16) conducted in pediatric patients. The mean duration of patients in hospital stay was 6.1 d which is similar to other studies assessing the antibiotic prescribing in pediatric patients (16,17). Antibiotic overuse may contribute to the development of resistance, treatment failure, and high health costs. The present study reveals that the percentage of patients who used antibiotics was 35.7 %, which is higher than The World Health Organization (WHO) standards (20.0-26.8%) (9). Antibiotic usage was reported higher in some studies made in Italy (49.9%) (18) and in India (79.4%) (19), whereas less (18.5%) and compatible with WHO standards in the studies conducted in Saudi Arabia (20,21,22). Cephalosporins, followed by penicillins were the most commonly used antibiotics in our study like other studies conducted in both pediatric and adult patients (16,17,23,24).

In our study, the culture test was performed in 15.8 % cases where 8.03 % cultures showed positive culture result, that is lower than in the Abbas et al. (17) study (42%) and higher than in Salameh K et al (25) study (2.42%). Though clinical parameters alone are not helpful for the prediction of bacteremia, patients' blood samples should be obtained for culture because the isolation of the causative organism directs the clinician to prescribe the optimal therapy (26).

The low percentage of culture testing could be due to a long waiting period (7 working days) for the results of the antibiogram test and urge of the physicians to start treating the infections as soon as possible, usually with broad-spectrum antibiotics.

The irrational use of combination therapy can worsen the already alarming scenario of antibiotic resistance and should be prescribed for critically ill patients with multidrug-resistant organisms. In this study, the inappropriate antibiotic combinations were found higher (26%) than the findings of Glowacki et al (27), who reported 16.1% of inappropriate antibiotic combinations in pediatric patients. When we evaluated the prescriptions according to indications in this study, we have seen that the percentage of antibiotics use in respiratory system infections, usually caused by viral agents, were high. However, physicians' diagnostic uncertainty can be one of the reasons for inappropriate prescribing because determining whether an infection is viral or bacterial might be clinically challenging (28,29).

We determined the convenience accurateness of antibiotic prescribing by additionally reporting the errors in dose frequency and administration route errors as well as indication and dosage.

We found that indication (25.88%), dose frequency (55.69%), administration route (16.08%) errors were higher than in other studies (30-33). However, a wrong dosage was found in 2.67 % of cases in this study, less than in the studies of Zeleke et al. (30) and Alanazi et al. (32) reported as 31.39 % and 28.7 %, respectively.

The variety in the frequency of prescribing errors might be associated with the difference in the training of the prescribers, numbers of patients included in the studies, and differences between the definition of prescribing errors (34,35).

Prescribing errors were generally the most frequent in the penicillins comparing to the other antibiotic groups in our study, while macrolides and cephalosporins in other studies (11,32).

The frequency of individual prescribing errors, dosage and dosing frequency errors were most frequent with penicillins while infusion duration errors with cephalosporins.

The 4 weeks-1-year-old patients were found to be using penicillins, cephalosporins and glycopeptides were higher comparing to the other age groups that lead to a conclusion that the patients in this age group were under the highest exposure of prescription errors including dosage, dosing frequency, infusion duration, and indication errors.

Due to the relation of inappropriate antibiotic administration and increasing rate of antibiotic resistance shown in many studies optimized antibiotic doses and administration patterns are essential for minimizing the emergence of resistant organisms (36,37).

The antibiotic use in pediatric clinics should be under the surveillance of a pediatric infectious disease specialist. However, the follow-up of the primary treating physician is of utmost importance, since the primary physician follows the case from diagnosis to discharge, and can observe clinical deterioration earlier. A well-organized prescription reporting system that could identify the causes of errors and assess the risk should be organized in the pediatric department. Additionally, the training programs on antibiotic therapy for both doctors and nurses may be effective to reduce the errors and to improve patient safety. The monitoring of antibiotic use continuously, adequate use of diagnostic tests may be also effective.

An active antibiotic stewardship program is also necessary to regulate the use of antibiotics and to reduce resistance. Antibiotic stewardship program includes the conscious use of antibiotics by healthcare professionals; means the selection of the most appropriate antibiotic, duration of treatment, drug dose, and route of administration for the patient in case of suspected infection. Antibiotic stewardship seeks to optimize clinical results by limiting the emergence and transmission of resistant bacteria. This program aims to use antibiotics in case of suspected infection, choosing the most appropriate antibiotic, treatment period, drug dose, and route of administration for the patient. Infectious disease specialist doctors, clinical pharmacists trained in infectious diseases, clinical microbiologists, information systems specialists, infection control professionals, and hospital epidemiologists are preferred for antibiotic stewardship programs (38,39).

Conclusion

The study showed that inappropriate use of antibiotics is a problem in pediatric patients. Inappropriate use was mostly in indication, dose frequency, and administration route. Another important point is that very little culture antibiogram tests have been performed. This is important for correct antibiotic selection and prevention of resistance. Rational antibiotic use is the basis for

reducing the emergence of bacterial resistance and several clinical problems. The increase of antibiotic resistance causes prolongation of hospital stay, increased mortality, and health care costs as a result of losing efficacy in clinical and community settings.

We think it would be beneficial to provide training in the form of courses or training meetings and applying active comprehensive antibiotic stewardship programs including the monitoring systems to avoid inappropriate use of antibiotics.

Limitations of the study: It is not a multi-center study and so has been conducted relatively in a small sample size.

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Availability of data: The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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Table 1. Demographic Characteristics and diagnosis of patients

Age groups	n (%)
0-4 weeks	23 (4.3)
4 weeks- 1 year	220 (41.12)
1-3 years	77 (14.39)
4-6 years	76 (14.21)
6-14 years	96 (17.94)
>14 years	43 (8.04)
Diseases	n (%)
Pulmonary diseases	264 (49.35)
Gastroenterology diseases	73 (13.64)
Central nervous system diseases	20 (3.74)
Hematological disease	15 (2.8)
Urinary system disease	68 (12.71)
Undiagnosed	48 (8.97)
Other diseases	47 (8.79)
Total	535 (100)

Table 2. The distrubition of prescribed antibiotic groups

Antibiotic group	n %
Penicilins	220 (28.28)
Penicilin G	6 (2.72)
Penicilin+Beta- lactamase inhibitor	16 (7.27)
Broad spectrum penicilin	195 (88.63)
Cephalosporins	352 (45.24)
First generation	5 (1.42)
Second genertation	10 (2.84)
Third generation	337 (95.7)
Macrolides	70 (9.0)
Carbapenems	39 (5.01)
Nitroimidazols	45 (5.78)
Aminoglycosides	15 (1.93)
Glycopeptides	27 (3.47)
Others	10 (1.29)

Table 3.

Frequency of
antibiotic
prescribing
according to age
groups

Antibiotic groups		0-4 weeks	4 weeks-1 year	1-3 years	3-6 years	6-14 years	>14 years	Total	P value
Penicillins	n%	17 (7.7)	116 (52.7)	31 (14.10)	20 (9.1)	26 (11.8)	10 (4.5)	220 (100)	0.000
Cephalosporins	n%	24 (6.8)	119 (33.8)	50 (14.2)	48 (13.6)	79 (22.4)	32 (9.1)	352 (100)	0.002
Nitroimidazoles	n%	0 (0.00)	18 (40)	6 (13.3)	6 (13.3)	12 (26.7)	3 (6.7)	45 (100)	0.195
Glikopeptids	n%	0 (0.00)	10 (0.37)	4 (0.15)	9 (0.33)	2 (0.07)	2 (0.07)	27 (1)	0.018
Aminoglycosides	n%	0 (0.00)	5 (0.33)	0 (0.00)	1 (0.07)	8 (0.53)	1 (0.07)	15 (1)	0.021
Carbapenems	n%	2 (5.1)	18 (46.2)	3 (7.7)	4 (10.3)	6 (15.4)	6 (15.4)	39 (100)	0.41
Macrolides	n%	7 (0.1)	29 (0.41)	10 (0.14)	5 (0.07)	14 (0.2)	5 (0.07)	70 (1)	0.62

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Table 4. The frequency of prescribing errors according to antibiotic groups

	Prescribing errors			
Antibiotic groups	Indication n (%)	Administration route n (%)	Dose frequency n (%)	Dosage n (%)
Penicilins	27 (12.27)	3 (1.36)	140 (63.63)	3 (1.36)
Cephalosporines	20 (5.68)	33 (9.37)	2 (0.56)	1 (0.28)
Nitroimidazoles	1 (2.22)	1 (2.22)	0	0
Glycopeptides	6 (22,22)	2 (7.41)	0	0
Aminoglycosides	2 (13.33)	1 (6.67)	0	0
Carbapenems	1 (2.56)	1 (2.56)	0	2 (5.13)
Macrolides	9 (12.85)	0	0	0
Total	66 (25.88)	41 (16.08)	142 (55.6)	6 (2.67)