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Antibiotic-associated Adverse Drug Events in Hospitalized Children

Hastanede Yatırılan Çocuklarda Antibiyotikle İlişkili Advers İlaç Olayları

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Abstract

Objective: Antibiotic use is high in patients hospitalized in the pediatric clinic. Side effects are common in association with antibiotic use. The aim of this study was to reveal antibiotic-associated adverse drug events (antibiotic-associated ADEs) in patients receiving inpatient treatment in the general pediatric clinic.

Material and Methods: File records of the patients hospitalized in the pediatric clinic of our hospital between June 2018 and October 2019 were retrospectively analyzed. Antibiotic-associated adverse drug events were recorded.

Results: One thousand three hundred and fifty cases were hospitalized in this period. Of these patients, 617 (45.7%) received antibiotics for at least 24 hours and were included in the analysis. A total of 152 cases, 51.3% (n= 78) girls and 48.7% (n= 74) boys, were included in the study. The ages of the cases ranged from 1 to 216 months, with a mean of 24.29 ± 38.6 months. Fifty-four percent of the cases with ADEs were followed up in the service with the diagnosis of acute lower respiratory tract infections, 21.7% bacteremia and sepsis, 20.2% urinary tract infections, and 2.7% skin and soft tissue infections. A total of 152 (24.6%) patients experienced ADE associated with at least one antibiotic. The most common antibiotics causing ADEs were 3rd generation cephalosporins (46.7%), ampicillin-sulbactam (21.7%) and aminoglycosides (9.9%). The most common side effects were determined as gastrointestinal system (63.9%), hepatobiliary system (16.5%), skin findings (9.2%) and anaphylaxis (6.6%), respectively.

Conclusion: Although antibiotics can play a critical role when used properly, it is necessary to start antibiotics according to the appropriate indications, especially due to our findings that can have severe consequences such as anaphylaxis. In addition, one should be alert in terms of side effects.

Keywords: Antibiotics, adverse effects, diarrhea, anaphylaxis

Öz

Giriş: Çocuk kliniğine yatırılan hastalarda antibiyotik kullanımı yüksektir. Antibiyotik kullanımına bağlı yan etkiler sık görülür. Bu çalışmanın amacı, genel pediyatri kliniğinde yatarak tedavi gören hastalarda antibiyotik ilişkili advers ilaç olaylarını (ADE) ortaya çıkarmaktır.

Gereç ve Yöntemler: Haziran 2018-Ekim 2019 tarihleri arasında hastanemiz çocuk kliniğinde yatan hastaların dosya kayıtları geriye dönük olarak incelenmiştir. Antibiyotikle ilişkili advers ilaç olayları kaydedilmiştir.

Bulgular: Bu dönemde hastaneye 1.350 vaka yatırılmıştır. Bu hastalardan 617 (%45.7)'si en az 24 saat antibiyotik almış ve analize dahil edilmiştir. Yan etki görülen olguların %51.3 (n= 78)'ü kadın, %48.7 (n= 74)'si erkek olmak üzere toplam 152 olgu çalışmaya dahil edilmiştir. Olguların yaşları bir ile 216 ay arasında değişmekte olup, ortalama 24.29 ± 38.6 ay olarak saptanmıştır. ADE'li olguların %54'ü akut alt solunum yolu enfeksiyonları, %21.7'si bakteriyemi ve sepsis, %20.2'si idrar yolu enfeksiyonları, %2.7'si deri ve yumuşak doku enfeksiyonları tanısı ile serviste takip edilmiştir. Toplam 152 (%24.6) hasta en az bir antibiyotik ile ilişkili ADE yaşanmıştır. ADE'lere en sık neden olan antibiyotikler üçüncü kuşak sefalosporinler (%46.7), ampisilin-sulbaktam (%21.7) ve aminoglikozidler (%9.9)'dir. En sık görülen yan etkiler sırasıyla gastrointestinal sistem (%63.9), hepatobiliyer sistem (%16.5), deri bulguları (%9.2) ve anafilaksi (%6.6) olarak belirlenmiştir.

Sonuç: Antibiyotikler doğru kullanıldığında kritik rol oynayabilse de, özellikle anafilaksi gibi ciddi sonuçları olabilen bulgularımız nedeniyle uygun endikasyonlara göre antibiyotik başlanması gerekmektedir. Ayrıca yan etkiler açısından da dikkatli olunmalıdır.

Anahtar Kelimeler: Antibiyotikler, yan etkiler, ishal, anafilaksi

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Introduction

Antibiotic use is extensively high in the world and in our country (1,2). According to the World Health Organization (WHO), "adverse drug reaction (ADR)" is defined as "a response to a drug that is noxious and unintended and occurs at doses normally used in men for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function" (3). Adverse drug events (ADEs) are common in hospitalization. These events may cause critical morbidity and mortality and financial costs (3). In adults, approximately 50% of hospitalized patients receive at least one antibiotic during their stay, and an estimated 20% to 30% of their hospitalization duration is considered unnecessary (3-6). When prescriptions of family medicine in Türkiye have been evaluated, it has been seen that 24.9% of the prescription in 2017 included at least one antibiotic (1). According to annual health statistics of 2019, antibiotic consumption 1.000 people in Türkiye was found as 35.3. This rate is quite higher when compared to the data of OECD countries (20.7 in 1.000) (7). According to WHO data, while the most commonly used oral antibiotics in Europe, where Türkiye is included, have been determined as amoxicillin and combination of amoxicillin/beta lactamase inhibitor, parenteral antibiotics have been found as ceftriaxone and gentamicin (8). Parenteral antibiotic use in hospitalized patients is common, and antibiotic-associated ADEs are frequently observed (9). In a study from Türkiye, the clinics with the highest rate of antibiotic use have been found as intensive care (100%) and pediatrics (65%) (10). There are not estimations regarding the incidence of antibiotic-related ADEs in hospitalized patients. In the most comprehensive study in the literature on adults on the current subject, ADE-associated with at least one antibiotic has been observed in 20% of hospitalized patients receiving antibiotic (2).

In general, there are not estimations regarding the incidence of antibiotic-related ADEs in hospitalized pediatric patients. In our study, it was aimed to present the development of antibiotic-related side effects in inpatients of our clinic.

Materials and Methods

This study is a retrospective cohort study comprising patients aged 1-18 years hospitalized in a tertiary academic public pediatric clinic between June 2018 and October 2019. Patients who had received oral/parenteral antibiotics for at least 24 hours were included into the study. Data of the patients with anamnesis were recorded. All side effects related to the antibiotic used during hospitalization were recorded and included in the study. Exclusion criteria were prophylactic antibiotic use with no clear cessation date, use of topical or inhaled antibiotics, tuberculosis regimens, and previously existing chronic diseases. Since our intensive care patients receive more antibiotics and have more than one comorbid disease, only patients admitted in the ward were included into the study. Demographic data, all pre-existing medical conditions, antibiotics regimens, and ADEs were collected through medical record review. Gastrointestinal, dermatologic, muscle-skeleton, hematologic, hepatobiliary, renal, cardiac, and neurological side effects were noted. Antibiotic-related side effects in patients were defined regarding the data in Table 1. Definitions were obtained from the literature, package insert, and/or consensus on the current study The denominator for calculations of general rates of ADEs included all patients receiving antibiotics. (n= 617). Preventable ADEs were defined as the rate of general ADEs that occur in patients considered not to be indicated for antibiotic use. We followed the method of the adult study of Tamma and colleagues to correlate ADEs

Table 1. Criteria used for antibiotic-associated adverse drug events

Adverse Drug Event	Definition
Non-*Clostridium difficile*-associated diarrhea	Loose stools associated with antibiotic administration and documented as "diarrhea" in the medical record, in the absence of laxative use or preexisting enteritis as descreibed in Bristol scale type 5-6. Patients with a positive *C. difficile* test result were excluded from this category
Nausea and vomiting	Nausea and vomiting associated with antibiotic administration, in the absence of an alternate explanation
Hepatobiliary	Cholestasis (total bilirubin level >1.5 mg/dL) or transaminitis (aspartate transaminase or alanine transaminase level >3 times patient's baseline) in the absence of existing hepatobiliary disease or recent biliary instrumentation
Hematologic	Anemia (hemoglobin level is below -2SD according to age and gender), leukopenia (white blood cell count <4500 cells/μL), or thrombocytopenia (platelet count $<150 \times 10^3$/μL) with levels below patient's baseline and in the absence of bleeding or myelosuppressive therapies
Renal	Increase in serum creatinine (the absence of precipitating factors for acute kidney injury such as the receipt of intravenous contrast or past kidney disease)
Dermatologic	Rash, including hives, nonhives rashes, and red man syndrome, temporally associated with antibiotic administration with resolution on antibiotic discontinuation; excluding vancomycin-associated red man syndrome
Cardiac	QTc >440 millisecond (ms) in males or >460 ms in females in the absence of preexisting arrhythmias, based on two electrocardiograms.
Anaphylaxis	World Allergy Organization Anaphylaxis Guidelines: Those diagnosed according to the 2013 evidence-based update.
Neurologic	Altered mental status, peripheral neuropathy, or seizures in the absence of preexisting neurologic conditions, or infectious syndromes

with antibiotics (2). Therefore, all potential ADEs were finalized within the context of the medical history and clinical course of the patient in order to be sure about the fact that each event is probably associated with antibiotics and to eliminate alternative explanations and categorize the ADEs appropriately. Afterwards, based upon the probability that a specific antibiotic causes a specific ADE and the temporary relation of ADE and antibiotic application, each ADE was associated with one antibiotic. For instance, acute kidney damage in a patient receiving vancomycin and ceftriaxone can be associated to vancomycin use. This step was followed to avoid calculating ADE incidence more than it actually was since a part of the patients in our cohort was receiving more than one antibiotic during their hospitalization. The limitation to our study could be the fact that we could not follow the side effects that may have occurred after discharge. This study was approved by the ethics committee of our hospital with decision number 2021/101.

Statistical Analysis

Statistical Package for Social Sciences (IBM Corp. 2012. IBM SPSS Statistics for Windows Version 21.0. Armonk, NY: IBM Corp.) and Microsoft Excel (MS Office 2010) were used for statistical analyses of the data. To present data, descriptive statistics like frequencies and percentages were used, and p value <0.05 was used for the statistical significance of the differences. In addition, logistic regression analysis and Pearson's R correlation were performed to find ADE-related factors.

Results

During the study, 1.350 children were followed in our pediatric ward. In this period, 1.350 cases were hospitalized. Of these patients, 617 (45.7%) received antibiotics for at least 24 hours and included into the analysis. A total of 152 cases, 51.3% girls (n= 78) and 48.7% boys (n= 74), in whom adverse side effects had been observed, were included into the study. Age of the patients ranged between one and 216 months, and mean age was 24.29 ± 38.6 months. The most common antibiotic treatment indications were acute respiratory tract infections (most frequently community-acquired pneumonia) (52.1%), urinary tract infections (15.4%), bacteremia and sepsis (9.2%), and skin and soft tissue infections (4.7%). The most common diagnoses in cases with ADE were acute lower respiratory tract infections (54%, n= 82), bacteremia and sepsis (21.7%, n= 33), urinary tract infections (20.2%, n= 31), and skin and soft tissue infections (2.7%, n= 4). The most common underlying comorbid diseases are presented in Table 2. Medi-

Table 2. Characteristics of the patients

Characteristics		ADEs		p	Total patient n/(%)*
		Yes n/(%)	No n/(%)		
Sex	Male	78 (23.8)	250 (76.2)	0.53	328 (53.2)
	Female	75 (26)	214 (74)		289 (46.8)
Most co-morbidities	Asthma and/or reactive airway disease				66 (10.7)
	Neurological diseases				15 (2.4)
	Congenital heart diseases				13 (2.1)
	Gastrointestinal diseases				6 (0.8)
	Metabolic diseases				4 (0.6)
	Down syndrome				4 (0.6)
Most antibiotic indications	Acute respiratory tract infections (most often community-acquired pneumonia)	82 (25,5)	239 (74,5)		321 (52.1)
	Urinary tract infections	32 (33.7)	63 (66.3)		95 (15.4)
	Bacteremia and sepsis	34 (59.6)	23 (40.4)	**0.0001**	57 (9.2)
	Skin and soft tissue infections	4 (13.8)	25 (86.2)		29 (4.7)
	Others	2 (1.7)	113 (98.3)		115 (18.6)
Number of antibiotics prescribed per patients	1	117 (25.5)	341 (74.5)		458 (74.2)
	2	71 (44.7)	88 (53.3)	**0.0001**	159 (25.8)
Most used antibiotics	Third generation cephalosporins	71 (29.5)	170 (70.5)		241 (39.1)
	Ampicillin + sulbactam	34 (23.9)	108 (76.1)		142 (23)
	Macrolides	13 (20.6)	50 (79.4)	0.28	63 (10.2)
	Aminoglycosides	16 (28.1)	41 (71.9)		57 (9.2)
	Ampicillin	12 (23.1)	40 (76.9)		52 (8.4)
	Others	10 (16.1)	52 (83.9)		62 (10.1)

*Percentages are calculated with respect to total ADEs (n= 617).

an length of hospital stay was five days (2-14 days). The most common antibiotics causing ADE development were third generation cephalosporin regimens (n= 71,%46.7), ampisilin + sulbactam (n= 33, %21,7), aminoglycoside regimens (n= 15-9, %9), and macrolide regimens (n= 12, %8) (Table 3). Of the patients, 25% (n= 8) received more than one antibiotic during hospitalization. Median day of treatment (DOT) per patient was 5 days (3-14 days). A total of 152 patients (24.6%) had at least one antibiotic-associated ADE. In addition, we thought that 67 of the antibiotic regimens (10.9) were not noted clinically and by laboratory. We found that antibiotics were most commonly used in the treatment of acute lower respiratory tract infections, like bronchiolitis, in which viral etiology was dominant. Six (8.9%) of 67 non-indicated antibiotic regimens were associated with one DE. Median time elapsed until ADE development was four days (1-8 days). The most commonly observed adverse side effects were in the gastrointestinal system (antibiotic-related diarrhea, 63.9%), hepatobiliary system (higher liver enzymes 16.5%), skin rash (9.2%), ana anaphylaxis (6.6%). Life-threatening adverse side effects like anaphylaxis were most commonly seen with cefotaxime (50%). Neurological adverse side effects, pancreatitis and myositis were not seen in in our pediatric patients (Table 3). ADE values were significantly higher in septicemia treatment and in the use of more than one antibiotic (p= 0.0001) (Table 2). Fortunately, antibiotic-dependent, ADE-related mortality was not found in our study.

Discussion

Unnecessary antibiotic use is particularly concerning since antibiotics may be related to a series of ADEs from allergic reactions, end organ toxicity to infection with antibiotic-resistant organisms (2,11,12). Most ADEs can be prevented since they occur as a result of drug errors in drug processing, prescribing, transcription, distribution, conformity or in any phase of drug monitoring (13).

It is possible for hospitalized patients to encounter more ADE due to various reasons. In a study from Türkiye, 63.2% of hospitalized patients have been reported to be under antibiotic treatment (14). In the USA, mean 69.464 emergency service visits were found annually in children aged under 19 years due to antibiotic-related side effects between 2011 and 2015. While 40.7% emergency service visits due to antibiotic-related side effects have constituted children aged under two years, allergic reactions have been reported at a rate of 86.1% (15). In a retrospective cohort study by Vaughn and colleagues (16), 67.8% of the patients have been reported to have received excessive antibiotic treatment. Most of these have been found to be comprised of antibiotics prescribed during discharge. Finally, in a study on adults, antibiotic initiation rate in hospitalized patients has been found as 27% (2). In our study, at

Table 3. Proportion of 152 patients receiving systemic antibiotic therapy who developed adverse drug events

Antibiotic Agent No (%)	No of Total ADEs	Gastrointestinal[c]	Hepatobiliary	Nonhives and hives rash.	Anaphylaxis	Renal	Hematologic	Cardiac	Other Events[a]	Total ADEs
Ceftriaxone	54 (35.5)	38 (70.4)	8 (14.9)	5 (9.2)	2 (3.7)	0	1 (1.8)	0	0	55 (100)
Cefotaxime	17 (11.2)	4 (23.6)	3 (17.6)	5 (29.4)	5 (29.4)	0	0	0	0	17 (100)
Ampicillin-sulbactam	33 (21.7)	28 (84.8)	4 (13.5)	0	1 (3.5)	0	0	0	0	33 (100)
Aminoglycosides	15 (9.9)	9 (60)	3 (20)	1 (6.7)	1 (6.7)	1 (6.7)	0	0	0	15 (100)
Ampicillin	11 (7.2)	6 (54.5)	4 (36.4)	0	1 (9.1)	0	0	0	0	11 (100)
Azithromycin	3 (2)	3 (100)	0	0	0	0	0	0	0	3 (100)
Clarithromycin	9 (6)	7 (77.8)	0	1 (11.1)	0	0	0	1 (11.1)	0	9 (100)
Clindamycin	2 (1.3)	0	0	2 (100)	0	0	0	0	0	2 (100)
Vancomycin	5 (3.2)	0	2 (40)	0	0	2 (40)	0	0	1 (20)	5 (100)
Meropenem	3 (2)	2 (66.7)	1 (33.3)	0	0	0	0	0	0	3 (100)
Total antibiotics[b]	152 (100)	97 (63.9)	25 (16.5)	14 (9.2)	10 (6.6)	3 (2)	1 (0.6)	1 (0.6)	1 (0.6)	152 (100)

[a]Other ADEs include vancomycin -associated red man (1), [b]Some patients [34 (22.4%] received more than 1 antibiotic, [c]Includes nausea, emesis, ve antibiotics-associated diarrhea.

least one antibiotic initiation rate of our inpatients was 45.7%. In fact, our rate is similar to other pediatric clinics but higher than adult clinics because many infections in adults can be treated as outpatients with oral antibiotics. It is natural for pediatric clinics to have higher antibiotic initiation rates since most children are admitted due to acute infections. Antibiotic-related ADEs are more common in pediatric patients when compared to adults (17).

Antibiotic-related ADEs are more common in inpatients when compared to outpatients. A reason for this is that high doses of intravenous antibiotics are administered to inpatients and these antibiotics may have different adverse effect profiles than more commonly prescribed oral antibiotics (2,18). Another reason is that more than one drug is frequently administered to inpatients, which potentially leads to a synergic increase in ADE development risk (2,19). In the literature, ADE assessment in children has been limited to single antibiotic classes or single infection syndromes (20). We, in our study, included all antibiotics and all diseases.

In the most comprehensive study conducted on adults in the literature, 73% of a total of 298 adverse effects have occurred on the first five days of hospitalization, and 27% have occurred within the first 30 days after discharge (2). There was no adverse effect that occurred after discharge. However, the side effects that have occurred in our country have been observed in the first four days.

ADE prevalence in inpatients in the UK, Germany and the USA has been found respectively as 3.2%, 4.8% and 5.6% (12). In addition, it has also been determined that presence of antibiotic-related ADE is an independent determinant of long-term hospitalization and total hospital cost (12). Researchers have found ADE in 20% of inpatients receiving antibiotic treatment for at least 24 hours (2). The findings showed that antibiotic-associated ADEs were detected in 38.9% of the patients in general. Antibiotic treatment for hours has developed antibiotic-associated ADE (20). Similar to our results, in a study from a tertiary hospital in Australia, antibiotic prescription has been found as the reason for antibiotic-associated unpreventable ADE in 29% of the total cases reported (21). In our study, antibiotic-associated ADE development was found as 24.6%, similar to other studies.

The most commonly used antibiotics in our study were respectively as third generation cephalosporins (46.7%), ampisilin + sulbactam (21.7%) and aminoglycosides (9.9%). While adverse side effects in adults have been associated with ceftriaxone, intravenous vancomycin and cefepime, a study including hybrid patients, the side effects have been associated with fluoroquinolones (11.8%), macrolides (11.65) and cephalosporins (10.9%) (2,20).

The most commonly observed adverse effects in our study were of the gastrointestinal system (63.9%). It was seen that in patients with antibiotic-associated diarrhea, the most common treatments were ceftriaxone (25%), ampisilin-sulbactam (18.4%) and macrolide (6.6%). We routinely start probiotics in our patients receiving antibiotics as it is mentioned in the guidelines. Anaphylaxis and maculopapular rash were seen most commonly after cefotaxime treatment (50%/35.7%, respectively). In a study by Tamma and colleagues (2) on 1.488 adult patients, antibiotic-associated side effects have been seen in 20% of the patients. The most common antibiotic side effects have been gastrointestinal (42%), renal (24%) and hematologic (15%), respectively. In a meta-analysis by Hum and colleagues (19) on the side effects of antibiotics used in the treatment of otitis media, diarrhea incidence has been found the lowest in azitromisin (2.2%) and the highest in amoxicillin/clavulanate (18.9%). In the same study, incidence of generalized rash has been determined the lowest in azitromisin (1.4%) and the highest in amoxicillin (6.5%). Similarly, in a study from India, the most commonly affected system in the body due to antibiotic-associated ADRs has been established as the gastrointestinal system (22). In a cross-sectional, multicenter study by Iftikhar et al. (17) on both adult and pediatric patients, it has been reported that gastrointestinal system was the most commonly affected system due to antibiotic-associated side effects with a rate of 38%. It has been emphasized that there were 486 side effects due to antibiotics, and most of them (43.6%) were preventable.

Another study has pointed out that approximately 40% of fluoroquinolone treatments in inpatients are unnecessary, and as a result, gastrointestinal events (14%), colonization with a multidrug-resistant organism infection (8%) and Clostridium difficile infections (CDIs) (4%) have developed (23). Finally, Macy and Contreras (24) have evaluated the incidence of cephalosporin-related ADEs, and they have found that the most commonly reported severe ADEs have been CDI that occur in nearly 1% of patients. Again, in a study, the researchers have determined that 19% of antibiotic regimens are not indicated and have been given due to asymptomatic bacteriuria treatment or non-infectious lower respiratory conditions. Twenty percent of the antibiotic regimens that are not indicated have been associated with one ADE (2). According to an estimation, approximately 50% of inpatients receive one antibiotic during their stay, and antibiotic use is not necessary in 20-30% of the cases (25,26). We considered that 10.9% of the patients who had been started on antibiotics were not indicated. Additionally, 8.9% of these patients were associated with an ADE. The need to use more than one antibiotic in pediatric patients is always lower than in the adults. In a study on adults, the rate of initiating more than one antibiotic in patients has been found as 79% (2). Initiating more than one antibiotic in

our patients was 25.8%. ADE development rate was higher in these patients, which indicated that we should be more careful with antibiotic combinations since they increase the risk of side effects unless necessary.

Findings of a meta-analysis have shown that 100.000 patients die due to ADR in the USA annually (21). Life-threatening ADEs like anaphylaxis is important. In the literature, 24% has been evaluated as severe to life-threatening (2). Anaphylaxis rate in our study was 6.6%. Again, in another study, every 10 DOT is additionally associated with a 3% ADE (2). Each extra day of treatment has been associated with a 5% increase in antibiotic-related side effects after discharge (20).

In a study, ADEs have been most commonly observed in females aged 18-52 years, patients with asthma and acute respiratory tract disease, and cases receiving more than two antibiotics (20). In a retrospective study on pediatric patients in China, development of ADEs has been significantly associated with the number of drugs, but not with age or sex (27). Major reason for this could be the fact that when multiple drugs are prescribed, drug interaction risk increases and leads to ADE development patients (28). Similar to the study from China, we found no relation between age, sex, antibiotics used and ADEs. However, we also observed more ADEs in patients receiving antibiotics for bacteremia/septicemia and in those receiving more than one antibiotic as in the studies found in the literature (2,21,27,29). The reason could be that we usually start dual treatment in these patients.

Scientific term covering the method to understanding, recognizing, and preventing ADEs is known as pharmacovigilance (30). The fundamental objective of pharmacovigilance is to prevent these adverse effects and ensure patient safety (31). Necessary correspondences were made as a result of pharmacovigilance assessment in our patients developing anaphylaxis.

One of the limitations of our study was patient follow-up. Our study was a single-center study in an academic institution. Our findings should be supported by larger studies from multicenter pediatric clinics and by studies that cover different disease groups. Since prescription of some antibiotics is sparse (for instance, clindamycin, vancomycin, meropenem), correct estimations of some drug-specific ADEs could not be calculated. Our hospital does not have a strong antibiotic management program. Therefore, we cannot say that we could completely show antibiotic-associated ADEs. Last, we could not detect the side effects that might have developed after discharge.

Conclusion

This study found that antibiotic-associated ADE developed in 24.6% of the patients hospitalized and treated with antibiotics for at least 24 hours. Side effects due to antibiotics are common in our clinical practice. These findings point to the importance of rational antibiotic use to diminish the harm that antibiotic-associated ADEs could do. Clinicians should have tehri eyes open for life-threatening side effects like anaphylaxis. In order to minimize side effects, community awareness must be raised in rational antibiotic use.

Ethics Committe Approval: Ethical approval was obtained from the İstanbul University of Health Sciences Sancaktepe City Prof. Dr. İlhan Varank Training and Research Hospital Ethics Committee (Decision no: 2021/104, Date: 10.02.2021).

Informed Consent: Patient consent was obtained.

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