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RESEARCH

Antibiotic-related adverse events and risk factors in hospitalized patients: a prospective cohort study

Hastanede yatan hastalarda antibiyotikle ilişkili advers olaylar ve risk faktörleri: prospektif kohort çalışması

Orçun Soysal[1], İrfan Şencan[2], Nesibe Korkmaz[3]

[1]Department of Infectious and Clinical Microbiology Diseases, Niğde Education and Research Hospital, Niğde, Turkey.
[2]Department of Infectious and Clinical Microbiology Diseases, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey.
[3]Department of Infectious and Clinical Microbiology Diseases, Ankara Etlik City Hospital, Ankara, Turkey.

Abstract

Purpose: The objective of this study is to identify antibiotic-related adverse events and risk factors in hospitalized patients.
Materials and Methods: This prospective cohort study included 776 inpatients who received antibiotic treatment between January 2019 and December 2020. Patients who experienced "definite" or "probable" adverse drug events (ADE) were examined using the World Health Organization-Uppsala Monitoring Center (WHO-UMC) criteria. The definition and severity criteria for antibiotic-related adverse events were determined according to the Common Terminology Criteria for Adverse Events (CTCAE).
Results: The overall rate of antibiotic-associated ADE was 7.9 (95%CI, 6.8-9.1) per 1000 person-days. The study identified a total of 152 adverse events in 125 patients who experienced ADE. Among the 152 adverse events, 63 (41.4%) were severe, and 89 (58.6%) were non-severe. Independent risk factors for ADE included the number of comorbidities (up to 4 times higher increased risk), number of drugs used, and duration of antibiotic administration (up to 12.3 times higher and 8% increased risk for each additional day). The most common side effects were hematological, with 45 (29.6%) cases reported in the hematological system advers events.
Conclusion: The management of antibiotic durations, which is a controllable factor in the development of antibiotic-related adverse events, is crucial. Rational use of antibiotics is essential, not only in terms of preventing the development of resistance but also in terms of reducing the frequency of adverse events that may become life-threatening.
Keywords:. Adverse event, antibiotics, risk factors

Öz

Amaç: Bu çalışmanın amacı, hastanede yatan hastalarda antibiyotikle ilişkili advers olayları ve risk faktörlerini belirlemektir.
Gereç ve Yöntem: Bu prospektif kohort çalışma, Ocak 2019 ile Aralık 2020 arasında antibiyotik tedavisi alan 776 yatan hastayı içermektedir. "kesin" veya "muhtemel" advers olay (AO) saptanan hastalar, Dünya Sağlık Örgütü-Uppsala İzleme Merkezi (DSÖ-UMC) kriterlerine göre incelenmiştir. Antibiyotikle ilişkili olumsuz olayların tanım ve ciddiyet kriterleri, Common Terminology Criteria for Adverse Events (CTCAE) kriterlerine göre belirlenmiştir.
Bulgular: Antibiyotikle ilişkili AO'ın genel oranı 1000 hasta günü başına 7.9 (95% CI, 6.8-9.1) idi. Çalışmada, AO yaşayan 125 hastada toplam 152 advers olayı tespit edildi. Bu 152 advers olayın 63'ü (%41.4) ciddi ve 89'u (%58.6) hafif advers olaylardı. AO için bağımsız risk faktörleri, komorbiditelerin sayısı (4 kat daha yüksek artmış risk), kullanılan ilaçların sayısı ve antibiyotik tedavisinin süresini (12.3 kat daha yüksek ve her ek gün için %8 artmış risk) içeriyordu. En yaygın yan etkiler hematolojikti ve hematolojik sistemde 45 (%29.6) olgu bildirilmişti.
Sonuç: Antibiyotik sürelerinin yönetimi, antibiyotikle ilişkili olumsuz olayların gelişiminde kontrol edilebilir bir faktör olduğu için kritiktir. Antibiyotiklerin rasyonel kullanımı, sadece direnç gelişimini önlemek açısından değil, aynı zamanda hayati risk taşıyabilecek olumsuz olayların sıklığını azaltmak açısından da önemlidir.

Anahtar kelimeler: Advers olaylar, antibiyotikler, risk faktörleri.

Address for Correspondence: Orçun Soysal, Department of Infectious and Clinical Microbiology Diseases, Niğde Education and Research Hospital, Niğde, Turkey.E-mail: orcunsysl@gmail.com
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INTRODUCTION

While antibiotics are generally considered safe drugs, their frequent use can lead to life-threatening adverse events[1]. Approximately half of hospitalized patients receive antibiotics during their hospitalization[2]. Predicting the frequency and severity of these events before initiating treatment is crucial for contributing to the pharmacoeconomy by reducing health-related costs, such as patient care costs, and lowering patient morbidity and mortality[3].

Although all antibiotics can cause adverse events, the probability is higher with specific agents in certain antibiotic groups. Various patient- and drug-related factors can increase the prevalence and severity of adverse events[4,5]. Among patient-related factors, age, gender, body weight, and comorbidities are notable, while polypharmacy and drug dosage are relevant drug-related factors[5-7].

In the realm of pharmacovigilance, the focus lies on monitoring, evaluating drug safety, and preventing drug-related hazards. This involves determining the frequency of suspected adverse reactions, establishing a cause-and-effect relationship between the event and the drug, and assessing severity. These studies may result in drug withdrawals from the market or modifications to licensing conditions and the Summary of Product Characteristics (SPC). Furthermore, the widespread promotion of rational antibiotic use and pharmacovigilance studies could potentially predict and reduce adverse events associated with antibiotics, consequently decreasing mortality and morbidity.

Data on the incidence of antibiotic-related adverse events in hospitalized patients are limited [8]. Existing pharmacovigilance studies usually focus on a single type or class of antibiotics. Therefore, our objective is to determine the occurrence rate of adverse events associated with antibiotic treatment in hospitalized patients. Patients in the infectious diseases ward often exhibit reduced physical performance due to their ongoing infections and may have multiple co-morbidities [9]. Since inpatients typically receive intravenous therapy and multiple antibiotics, their likelihood of experiencing adverse events is influenced by these factors. This study aims to identify risk factors for adverse events in these patients, enabling us to anticipate and prevent such occurrences. We believe our study is unique as it examines patients receiving various antibiotic groups, setting it apart from other studies.

MATERIALS AND METHODS

The study employed a prospective cohort design within a tertiary healthcare institution boasting a 760-bed capacity. The case group comprised patients who underwent antibiotic treatment and subsequently developed adverse events, while the control group included patients who received antibiotic treatment without encountering adverse events. The study included patients aged 18 and above who received either oral or intravenous anti bacterial antimicrobial treatment in the infectious diseases ward between January 1, 2019, and December 31, 2020.

To maintain the specific focus of our study on patients receiving intravenous (IV) and oral antibacterial antibiotic treatment, individuals using antiviral, antifungal, antiparasitic, topical, or inhaler antimicrobial agents were excluded from participation.

The ethics for the study titled "Comparison of Antibiotic-Related Adverse Events in Patients Hospitalized in the Infectious Diseases Ward" were approved by the Ethics Committee of Dışkapı Training and Research Hospital on June 14, 2021. (Decision number:113/15).

Data collection and definitions

The patients who were identified as having "definite" or "probable" adverse drug events (ADE) according to the World Health Organization - Uppsala Monitoring Center (WHO-UMC) criteria [10]. Demographic information, such as age, gender, presence and number of comorbidities, number of drugs used at the beginning of antibiotic treatment, and basal levels of creatinine (Cre), white blood cell count (WBC), aspartate aminotransferase (AST), and alanine aminotransaminase (ALT), was recorded for these patients.

Additionally, we documented the responsible antibiotic for the ADE, the duration of antibiotic administration, and the purpose of the treatment. However, given that many patients received a combination of antibiotics, we determined the association of ADEs with the appropriate antibiotic based on existing literature data to prevent an overestimation of ADE incidence [8]. In cases where

adverse reactions occurred in patients receiving combined treatment, we associated the ADE with the antibiotic most likely to have caused it. For example, if a patient treated with both meropenem and vancomycin developed kidney injury, we attributed the ADE to vancomycin alone. Nevertheless, if a few of the administered antibiotics were ADE-specific, they were associated with all related antibiotics. The regression of adverse events following the discontinuation of antibiotics was also considered as a controlling factor [10].

As the assessment of severity index in adverse events is a relative concept, we determined the severity index by employing the criteria outlined in the CTCAE (Common Terminology Criteria for Adverse Events) guideline. According to the CTCAE guideline, events with a grade of 3 or higher were considered serious, while events with a grade of 2 or lower were considered mild adverse events [11].

The criteria determined for ADE are provided in Table 1.

Table 1. The criterias determined for ADE

ADE	Criteria
Hypersensitivity events	Dermatological: It can be in a wide scale from mild urticaria to Steven-Johnson Syndrome, Red man syndrome – seen in association with antibiotic administration- Drug Fever: Fever that cannot be attributed to any other cause and regresses within 72 hours after the drug is discontinued. It may be accompanied by rash, eosinophilia, and relative bradycardia. It should be supported by a negative blood culture. Anaphylaxis: Developing within minutes after antibiotic administration
Hematological events	Anemia: Hemoglobin level <10 g/dL Leukopenia: White blood cell count (WBC) <4500 cells/μL Thrombocytopenia: Platelet count <150.000 cells/ μL
Gastrointestinal system (GIS) events	Diarrhea: >3 defecations – Without active enteritis or laxative use – Nausea and Vomiting: It started after antibiotics and cannot be attributed to other causes. Dyspeptic complaints: unexplained by other causes
Hepatobiliary events	Cholestasis: Total Bilirubin level >2 mg/dL Hepatitis: AST and ALT > 3 times normal -Without active hepatobiliary disease to explain in the patient- International Correction Ratio (INR)>1.2
Renal events	Serum creatinine value >1.5 times patient basal level -Without other risk factors (Sepsis, use of other nephrotoxic substances such as contrast agent use) for acute renal failure-
Neurological events	Consciousness alteration, Peripheral Neuropathy, Epilepsy, Ototoxicity -Unexplained for other reasons-
Cardiac events	Prolonged QTc: >440 ms for male, >460 ms for female
Musculoskeletal events	More than 5-fold increase in serum Creatine Kinase, not due to myopathy or statin use

Statistical analysis

95% confidence intervals and rates per 1.000 person-days were calculated for every ADE. For each ADE, the numerator represented the count of ADEs attributed to a specific antibiotic, while the denominator was the risk for all patients, measured in person-time, who received that particular antibiotic. This measurement was calculated from the initiation of antibiotic treatment to the occurrence of the ADE, measured in days, for patients who experienced an ADE. To compare the distribution of categorical variables, we used the chi-squared test. If the expected number of observations in any category was less than 5, we applied Fisher's exact chi-square test. For assessing the difference between means in independent samples, we employed Student's t-test. When dealing with data that did not follow a normal distribution, the Mann-Whitney U test was utilized.

Furthermore, we conducted a multivariable analysis to assess the independent effects of clinically significant and notable risk factors identified in the univariate analysis. The logistic regression model included variables such as age, days of antibiotic exposure, and the number of additional diseases. We calculated odds ratios and their accompanying 95% confidence intervals for each variable. A statistically significant p-value was considered as <0.05."

RESULTS

The mean age of the 776 patients who received antibiotic treatment was 58 (18-94) years, with 431 (55.5%) being male. A total of 523 (67.4%) patients had at least one comorbid disease, with hypertension (HT) being the most common in 327 (42.1%) patients, followed by diabetes mellitus (DM) in 279 (35.8%) patients. Overall, 2040 antibiotic regimens were administered to the 776 patients, including antibiotic combinations and changes in regimens. The most prescribed antibiotics were piperacillin/tazobactam (n=301, 14.7%), meropenem (n=279, 13.6%), and ceftriaxone (n=273, 13.3%).

ADEs were detected in 125 (16.1%) of the 776 patients who received antimicrobial treatment. The patients with ADE had a mean age of 65 (20-90), and 77 (61.6%) of them were male. A total of 103 patients (82.4%) had at least one comorbid disease, with DM being the most common in 77 (61.6%) patients, followed by HT in 76 (60.8%) patients. The mean length of hospital stay of patients with ADE was 23.8 ± 13.4 days. Of those with ADE, 80 (64.0%) patients were treated for 15 days or more, 33 (26.4%) patients were treated for 8-14 days, and 12 (9.6%) patients were treated for 7 days or less. At the beginning of antibiotic treatment, 48 (38.4%) of them had more than 5 additional drugs. Diabetic foot infection was the most commonly treated disease in patients with ADE (n=23, 18.4%), followed by urinary tract infection (n=21, 16.8%) and infective endocarditis (n=17, 13.6%). The demographic data of both groups and the univariate analysis for risk factors are presented in Table 2.

Table 2. Demographic data of patients and the univariate analysis for risk factors

Variables	Patients with ADE n=125		Patients without ADE n=651		RR (%95 CI)	p Value
	n	%	n	%		
Gender						
Male	77	17.9	354	82.1	1.3 (0.9-1.8)	0.137
Female	48	13.9	297	86.1		
Age						
<40 years	13	9.6	122	90.4	1	
40-64 years	48	15.4	263	84.6	1.6 (0.9-2.9)	0.099
≥65 years	64	19.4	266	80.6	**2.1 (1.2-3.5)**	**<0.001**
Mean±SD	61.1± 16.3		58.1±18.6		-	0.066
Duration of Antibiotic Administration (day)						
≤7	12	4.2	276	95.8	1	
8-14	33	11.8	247	88.2	**2.8 (1.5-5.4)**	**<0.001**
≥15	80	38.5	128	61.5	**9.2 (5.2-16.5)**	**<0.001**
Median (Min-Max)	19 (5-46)		10 (1-45)		-	**<0.001***
Co-morbidity						
Exist	103	19.7	420	80.3	**1.14 (1.07-1.20)**	**<0.001**
None	22	8.7	231	91.3	1	
Number of co-morbidities						
None	22	8.7	231	91.3	1	
1 disease	21	10.7	176	89.3	1.2 (0.7-2.2)	0.482
2 diseases	34	19.1	144	80.9	**2.2 (1.3-3.6)**	**0.002**
≥3 diseases	48	32.4	100	67.6	**3.7 (2.4-5.9)**	**<0.001**
Number of drugs in use at antibiotic initiation						
None	19	7.0	254	93.0	1	
1-4 drugs	58	17.0	283	83.0	**2.4 (1.5-4.0)**	**<0.001**
≥5 drugs	48	29.6	114	70.4	**4.3 (2.6-7.0)**	**<0.001**

ADE: Adverse drug events RR: Relative risk CI: Confidence interval *****Mann-Whitney U test

In the multivariate analysis, the number of comorbidities and the number of drugs used by patients at the beginning of antibiotic treatment were evaluated in separate models due to their correlation, to avoid statistical errors. When age and number of comorbidities were evaluated, the risk of ADEs was found to be 12.3 times higher (p<0.001, 95% CI: 6.4-23.6) for those who were exposed to antibiotics for 15 days or more, as shown in Table 3. Additionally, it was found that the risk of ADEs increased by 8% with each additional day of antibiotic administration (p<0.001, 95% CI: 1.06-1.10).

Table 3. The risk factors causing adverse events, multivariate analysis

Risk Factors	OR_{adj} (95 CI)	SE	P
Age			
<40	Ref		
40-64	0.9 (0.4-1.9)	0.391	0.785
≥65	0.9 (0.4-2.1)	0.423	0.804
Number of Comorbidities			
No comorbidities	Ref		
1 disease	1.1 (0.6-2.2)	0.339	0.703
2 diseases	1.9 (1.1-3.6)	0.313	0.034
≥3 diseases	4.0 (2.2-7.3)	0.306	<0.001
Duration of Antibiotic Administration (day)			
≤7	Ref	-	
8-14	2.6 (1.3-5.2)	0.354	0.007
≥15	12.3 (6.4-23.6)	0.333	<0.001
Constant	0.003	0.352	<0.001

OR_{adj}: Adjusted odds ratio, SE: Standard error, Ref: Reference

When evaluating the effects of age and duration of antimicrobial exposure, the risk of adverse events was found to increase 2.2 times (p<0.001, 95% CI: 1.2-3.9) in patients who used 1-4 drugs, and 4.3 times (p<0.001, 95% CI: 2.3-8.0) in those who used 5 or more drugs, as shown in Table 4.

Table 4. Risk factors leading to adverse events, multivariate analysis

Risk Factors	OR_{adj} (95 CI)	SE	p
Age			
<40	Ref		
40-64	0.8 (0.4-1.7)	0.388	0.605
≥65	0.9 (0.4-1.9)	0.409	0.865
Number of Drugs Used When Antibiotic Treatment was Initiated			
0 drug	Ref		
1-4 drug	2.2 (1.2-3.9)	0.293	0.007
≥5 drug	4.3 (2.3-8.0)	0.313	<0.001
Duration of Antibiotic Administration (day)			
≤7	Ref		
8-14	2.6 (1.3-5.2)	0.353	0.006
≥15	12.2 (6.3-23.3)	0.332	<0.001
Constant	0.023	0.360	<0.001

OR_{adj}: Adjusted odds ratio, SE: Standard error, ref: Reference

A total of 152 adverse events were detected in 125 patients who received antimicrobial treatment in the study. Among the 152 adverse events, 63 (41.4%) were severe adverse events, and 89 (58.6%) were non-severe adverse events. The overall rate of antibiotic associated adverse events was 7.9 (95% CI, 6.8-9.1) per 1000 person-days. The most common adverse events were hematological reactions (n=45, 29.6%), hypersensitivity reactions (n=28, 18.4%), and hepatobiliary reactions (n=27, 17.8%). The percentile distribution of each adverse event is shown in Figure.

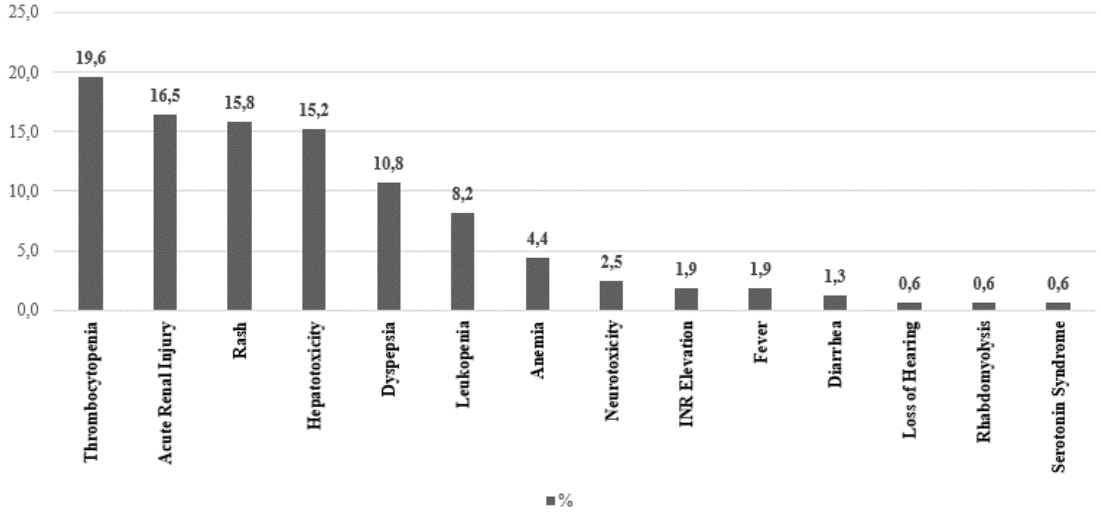

Figure1. Percentile distribution of the adverse events

The nephrotoxic effects of vancomycin, gentamicin, and colistin were found to be high, with rates of 22.0 (95% CI, 12.2-36.6), 44.5 (95% CI, 19.5-88.2), and 210.5 (95% CI, 97.7-399.8) per 1000-person days, respectively. Confusion developed in 2 out of 9 patients using cefepime, with a rate of 44.4 (95% CI, 7.4-146.8) per 1000-person days. For trimethoprim/sulfamethoxazole and doxycycline use, 34.1 (95% CI, 10.8-82.4) and 14.2 (95% CI, 2.3-47.2) episodes of hepatotoxicity were observed per 1000-person days, respectively as shown in Table 5.

Table 5. Rates of adverse drug events in 776 patients receiving antibiotics per 1000-person days

ADE	Antibiotics	Number of ADE*	Antibiotics DOT**	Rate per 1000 person day (95% CI)
Thrombocytopenia	Trimethoprim/sulfamethoxazole	1	117	8.547 (0.4276- 42.15)
	Linezolid	24	1441	1.666 (1.092- 2.44)
	Piperacillin/tazobactam	13	1977	6.576 (3.657- 10.96)
	Cefazolin	1	318	3.145 (0.1573- 15.51)
Skin rash	Ampicillin/sulbactam	3	1320	2.273 (0.5781- 6.185)
	Daptomycin	6	880	6.818 (2.763- 14.18)
	Ertapenem	1	437	2.288 (0.1145- 11.29)
	Imipenem	2	312	6.41 (1.075- 21.18)
	Meropenem	9	2648	3.399 (1.658-6.237)
	Piperacillin/tazobactam	2	1977	1.012 (0.1696- 3.342)
	Ceftriaxone	3	2541	1.181 (0.3003- 3.213)
	Ciprofloxacin	4	611	6.547 (2.08- 15.79)
	Vancomycin	2	591	3.384 (0.5674- 11.18)
Hepatotoxicity	Ampicillin/sulbactam	2	1320	1.515 (0.254- 5.006)
	Trimethoprim/sulfamethoxazole	4	117	34.19 (10.86- 82.47)
	Doxycycline	2	140	14.29 (2.395- 47.2)
	Imipenem	1	312	3.205 (0.1604- 15.81)
	Meropenem	1	2648	0.377 (0.018- 1.863)
	Piperacillin/tazobactam	6	1977	3.035 (1.23- 6.312)
	Ceftriaxone	5	2541	1.968 (0.721- 4.362)
	Ciprofloxacin	2	611	32.73 (0.5488- 10.81)
	Cefaperazone/sulbactam	1	123	8.13 (0.4068- 40.1)

	Tigecycline	1	458	2.183 (0.1092- 10.77)
Nephrotoxicity	Gentamicin	7	157	44.59 (19.5- 88.2)
	Colistin	8	38	210.5 (97.77- 399.8)
	Cefazolin	1	318	3.145 (0.1573- 15.51)
	Vancomycin	13	591	22.0 (12.23- 36.67)
Dyspepsia	Levofloxacin	1	378	2.646 (0.1324- 13.05)
	Linezolid	1	1441	0.694 (0.034- 3.423)
	Piperacillin/tazobactam	2	1977	1.012 (0.1696- 3.342)
	Ceftriaxone	2	2541	0.7871 (0.132- 2.6)
	Ciprofloxacin	1	611	1.637 (0.081- 8.072)
	Tigecycline	8	458	17.47 (8.112- 33.17)
Leukopenia	Trimethoprim/sulfamethoxazole	1	117	8.547 (0.4276- 42.15)
	Linezolid	3	1441	2.082 (0.5296- 5.666)
	Piperacillin/tazobactam	10	1977	5.058 (2.569- 9.016)
Anemia	Trimethoprim/sulfamethoxazole	1	117	8.547 (0.4276- 42.15)
	Linezolid	2	1441	1.388 (0.2327- 4.586)
	Piperacillin/tazobactam	3	1977	1.517 (0.386- 4.13)
Drug fever	Trimethoprim/sulfamethoxazole	1	117	8.547 (0.4276- 42.15)
	Meropenem	1	2648	0.3776 (00.18- 1.863)
	Vancomycin	1	591	1.692 (0.084-8.345)
INR Elevation	Cefazolin	2	318	6.289 (1.054- 20.78)
	Cefaperazone/sulbactam	1	123	8.13 (0.406- 40.1)
Confusion / epilepsy	Sefepim	2	45	44.44 (7.451-146.8)
	Imipenem	1	312	3.205 (0.1604- 15.81)
	Klaritromisin	1	358	2.793 (0.1398- 13.78)
Diarrhea	Ampicillin/sulbactam	1	1320	0.757 (0.0379- 3.73)
	Gentamicin	1	157	6.369 (0.3187- 31.41)
	Meropenem	1	2648	0.377 (0.0189- 1.86)
	Ciprofloxacin	1	611	1.637 (0.08189- 8.072)
Ototoxicity	Amikasin	1	48	20.83 (1.042- 102.7)
CK Elevation	Daptomycin	1	880	1.136 (0.05686-5.604)
Serotonin syndrome	Linezolid	1	1441	0.694 (0.0347- 3.423)

* ADE: Adverse Drug Events -In our study, 152 ADEs were developed, but as it is mentioned in methodology, some ADEs were attributed to two drugs. **DOT: Days of theraphy

DISCUSSION

The study revealed that the number of comorbidities was found to be an independent risk factor for the development of ADEs. Previous studies by Guzman et al., Saedder et al., and Otero et al. have similarly reported an increased risk of ADEs in patients with multiple comorbidities [12-14]. However, in those studies, the increased risk was associated with longer hospitalization. In contrast, our study controlled for the duration of antibiotic administration and found that the number of comorbidities remained an independent risk factor. Polypharmacy, as shown in numerous studies, including ours, has been linked to an increased frequency of ADEs [15, 16]. However, the relationship between polypharmacy and adverse events is complex, and clinical context factors such as drug interactions and comorbidity burden should also be considered.

It was found that 64% of those who developed adverse events had received antibiotics for 15 days or more. Each additional day of antibiotic administration increased the risk of adverse events by 8%, making it a major risk factor. A retrospective cohort study by Tamma et al. demonstrated that every 10-day increase in antibiotic administration raised the risk of adverse events by 3% [8]. Curran et al.'s meta-analysis also revealed that each additional day of antibiotics increased the risk of adverse events by 9% [17]. Lin et al. reported that prolonged antibiotic treatment and hospitalization were independent risk factors for adverse events [18]. In our study, for example, the majority (62.5%) of linezolid-associated thrombocytopenia occurred after the 15th day of treatment. Numerous studies have reported that the duration of treatment is directly associated with linezolid-associated thrombocytopenia [19, 20]. Benli et al. found that the incidence of leukopenia was 10% in

patients treated with piperacillin-tazobactam for longer than 10 days [21]. In our study, it was found that as the days of antibiotic exposure increased, the frequency of observed side effects significantly increased, which aligns with the limited data available in the literature. To delve into the reasons behind this phenomenon, more detailed antibiotic-specific studies are required. However, while addressing these effects, our primary concern should be to prevent inappropriate and prolonged antibiotic treatments. Thus, the risk of adverse events must be monitored more frequently in patients receiving prolonged treatment. Clinicians must consider the benefits and harms of treatment when deciding on the duration of antibiotic therapy for their patients. Shortening the duration of antibiotic treatment as much as possible is likely to reduce the incidence of adverse events significantly.

We often observe ongoing antibiotic treatments, particularly after surgical prophylaxis, in the unit where we work. Cefazolin is frequently used as a prophylactic treatment in surgical clinics. In our study, we identified adverse effects such as an elevated INR and thrombocytopenia as a result of cefazolin treatment. Cefazolin-associated coagulation disorders are not commonly encountered in the literature. However, there are case series reporting that vitamin K deficiency was the cause of increased INR levels [22-24]. It should be noted that this drug should not be used without a proper indication, especially after prophylaxis.

We observed another antibiotic side effect that caught our attention, which was neurotoxicity secondary to cefepime in 2 out of 9 patients. The frequency of neurotoxicity in the cefepime SPC is listed as "unknown." Tanaka et al. reported the incidence of cefepime-associated neurotoxicity as 2.73% [25]. Clinicians should keep cefepime-associated neurotoxicity in mind, especially in patients with kidney dysfunction.

Although 41.4% (n=63) of the adverse events were classified as serious adverse events, 58.6% (n=89) were classified as mild adverse events. In a study conducted by Courjon et al. on antibiotic side effects, 56 (37.0%) of the 151 adverse events detected were severe and 95 (63.0%) were mild [26]. However, this was the only literature we could find that reported the incidence of severity of antibiotic-related adverse events. This deficiency in the literature may be due to the lack of guidelines for categorizing severity criteria. In our study, the rate of severe adverse events in 2 out of the 5 identified cases is a noteworthy figure. Considering this rate, we believe that the risks associated with unnecessary antibiotic use become even more striking. In a study conducted by Werner et al., it was found that 39% of patients receiving fluoroquinolone treatment were unnecessarily prescribed antibiotics [27]. We are of the opinion that the importance of rational antibiotic use, primarily through educational initiatives, should be taken seriously and regulated by infection specialists, with active involvement from all clinicians.

The present study is one of the limited number of studies in the literature examining antibiotic-associated adverse events and their risk factors in hospitalized patients. However, several limitations exist. Firstly, due to its observational design, there was no placebo group. Secondly, the distribution of antibiotics was not homogeneous. Thirdly, late-term adverse events such as superinfection and drug resistance could not be evaluated since patients were not followed up after the end of antibiotic treatment.

The correct use of antibiotics has critical importance in the treatment of infectious diseases. However, predicting the adverse events that might occur due to these antibiotics is equally important. The growing awareness of reporting adverse events is of paramount importance in both identifying and anticipating such undesirable situations. Moreover, we anticipate that the rise in such reports may contribute to an increase in pharmacovigilance studies, which have been limited in the existing literature.

The number of comorbidities and the number of drugs used before the treatment, which are identified as risk factors, are parameters that cannot be altered. Nevertheless, these parameters aid in making a more careful decision regarding the adverse events that might arise from the treatment being considered. The day of exposure to antibiotics, identified as a major risk factor, is particularly crucial as it is at the discretion of the clinician. The importance of rational antibiotic use lies not only in preventing the development of resistance but also in reducing the incidence of adverse events, some of which may be life-threatening.

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