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Invisible Patient Safety Risk: A Point Prevalence Analysis of Antimicrobial-Related Potential Drug-Drug Interactions in Hospitalized Patients

Görünmeyen Bir Hasta Güvenliği Riski: Hastanede Yatan Hastalarda Antimikrobiyal ile İlişkili Potansiyel İlaç-İlaç Etkileşimlerinin Nokta Prevalans Analizi

© Nazife Duygu Demirbaş¹, © Hakkı Meriç Türkkan¹, © Okan Derin^{1,2}

¹University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İstanbul, Türkiye

²Epidemiology PhD Program, Istanbul Medipol University, Graduate School of Health Sciences, İstanbul, Türkiye

Abstract

Introduction: Antimicrobial-related potential drug-drug interactions (pDDIs) represent an important yet often underrecognized patient safety concern among hospitalized patients, particularly those receiving multiple medications. This study assessed the point prevalence, risk factors, and distribution of antimicrobial-related pDDIs among hospitalized adult patients.

Materials and Methods: This cross-sectional point prevalence study was conducted on March 4, 2026, at Şişli Hamidiye Etfal Training and Research Hospital. Adult inpatients receiving at least 1 systemic antimicrobial agent and at least 1 additional systemic medication were included. Potential drug-drug interactions were assessed using the UpToDate® Lexicomp® Drug Interactions Online Database. Interactions classified as category C, D, or X were considered pDDIs. Univariable and multivariable logistic regression analyses were performed to identify independent predictors of pDDIs.

Results: Among the 375 included patients, at least 1 antimicrobial-related pDDI was identified in 112 patients (29.9%). A total of 205 pDDI pairs were detected, of which 68% were category C (monitor therapy), 27% were category D (consider therapy modification), and 5% were category X (avoid combination) interactions. Overall, ceftriaxone (n=44), clarithromycin (n=33), and levofloxacin (n=18) were the most frequently implicated agents. Clinically higher-risk category D and X interactions were predominantly associated with clarithromycin (n=18), cefuroxime axetil (n=17), linezolid (n=9), and quinolones overall (n=7). In the multivariable logistic regression analysis, the total number of medications was the strongest independent predictor of pDDIs (odds ratio, 1.40; 95% confidence interval, 1.28-1.54; p<0.001).

Conclusion: Antimicrobial-related pDDIs were identified in 29.9% of hospitalized adult patients, with 32% of the identified pDDI pairs classified as category D or X interactions. Higher-risk interactions were predominantly associated with clarithromycin, cefuroxime axetil, linezolid, and quinolones. Routine screening for antimicrobial-related DDIs should be integrated into antimicrobial stewardship programs to enhance medication safety, particularly for patients receiving multiple medications.

Keywords: Drug interactions, anti-bacterial agents, polypharmacy, patient safety



Address for Correspondence/Yazışma Adresi: Nazife Duygu Demirbaş, MD, University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İstanbul, Türkiye

E-mail: naz_dyg@hotmail.com **ORCID ID:** orcid.org/0000-0002-0760-7740

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Öz

Giriş: Antimikrobiyal ile ilişkili potansiyel ilaç-ilac etkileşimleri (piİE), özellikle polifarmasi varlığında, hastanede yatan hastalarda önemli ancak sıklıkla gözden kaçan bir hasta güvenliği sorunudur. Bu çalışmada, hastanede yatan erişkin hastalarda antimikrobiyal ile ilişkili piİE'lerin nokta prevalansı, risk faktörleri ve dağılımının değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Bu kesitsel nokta prevalans çalışması, 4 Mart 2026 tarihinde üçüncü basamak bir eğitim ve araştırma hastanesinde gerçekleştirildi. En az bir sistemik antimikrobiyal ajan ile birlikte en az bir ek sistemik ilaç kullanan erişkin yatan hastalar çalışmaya dahil edildi. Potansiyel ilaç-ilac etkileşimleri, UpToDate® Lexicomp® Drug Interactions Online Database kullanılarak değerlendirildi. C, D ve X kategorisindeki etkileşimler piİE olarak kabul edildi. piİE gelişimiyle ilişkili bağımsız belirleyicileri saptamak amacıyla tek değişkenli ve çok değişkenli lojistik regresyon analizleri yapıldı.

Bulgular: Çalışmaya dahil edilen 375 hastanın 112'sinde (%29,9) en az bir antimikrobiyal ile ilişkili piİE saptandı. Toplam 205 piİE çifti tespit edildi; bunların %68'i C kategorisi (tedavinin izlenmesi önerilen), %27'si D kategorisi (tedavide değişiklik yapılması önerilen) ve %5'i X kategorisi (kombinasyondan kaçınılması gereken) etkileşimlerden oluşuyordu. Genel olarak en sık ilişkili ajanlar seftriakson (n = 44), klaritromisin (n = 33) ve levofloksasin (n = 18) iken; klinik açıdan daha yüksek riskli D ve X kategorisi etkileşimlerde klaritromisin (n = 18), sefuroksim aksetil (n = 17), linezolid (n = 9) ve kinolonlarla (toplam n = 7) ilişkiliydi. Çok değişkenli lojistik regresyon analizinde toplam ilaç sayısı, piİE gelişiminin en güçlü bağımsız belirleyicisi olarak saptandı (olasılık oranı: 1,40, %95 güven aralığı: 1,28-1,54; p < 0,001).

Sonuç: Antimikrobiyal ile ilişkili piİE'ler, hastanede yatan erişkin hastaların %29,9'unda saptanmış olup, belirlenen etkileşimlerin %32'si D veya X kategorisinde sınıflandırıldı. Klinik açıdan daha önemli D ve X kategorisi etkileşimler özellikle klaritromisin, sefuroksim aksetil, linezolid ve kinolonlarla ilişkiliydi. Bu bulgular, özellikle çoklu ilaç kullanan hastalarda antimikrobiyal ilişkili ilaç-ilac etkileşimlerinin sistematik olarak taranmasının, antimikrobiyal yönetim ve hasta güvenliği uygulamalarının önemli bir bileşeni olması gerektiğini göstermektedir.

Anahtar Kelimeler: ilaç etkileşimleri, antibakteriyel ajanlar, polifarmasi, hasta güvenliği

Introduction

Drug-drug interactions (DDIs) are conditions in which concomitantly administered medications alter each other's pharmacokinetic or pharmacodynamic properties, resulting in changes in drug efficacy or toxicity^[1,2]. A potential DDI (pDDI) refers to the concomitant use of 2 or more drugs with the potential to interact with one another^[3]. Therefore, pDDIs do not necessarily result in clinically higher-risk interactions, and the proportion that progresses to actual DDIs may vary. DDIs are among the major causes of adverse drug reactions and are associated with increased morbidity and mortality, prolonged hospital stays, and higher healthcare costs^[4,5]. Previous studies have reported that at least 1 pDDI has been identified in approximately one-third of hospitalized patients and in more than half of patients in intensive care units^[3].

This risk is particularly pronounced during antimicrobial therapy. Antimicrobials, which are widely used in hospital settings, represent an important risk group for pDDIs because of their frequent use in combination with multiple medications. Agents such as quinolones, triazole antifungals, macrolides, and linezolid may cause clinically significant interactions, including QT prolongation, serotonin syndrome, and nephrotoxicity^[6-9].

The frequency and clinical significance of antimicrobial-related pDDIs vary according to the study population, methodology, and interaction database used. Previous studies have reported that antimicrobials account for a substantial proportion of DDIs, with this contribution being particularly pronounced

among patients in intensive care units^[10]. Data from Türkiye indicate that antimicrobials account for approximately one-quarter of all drug interactions and that a limited number of agents, including quinolones, triazole antifungals, metronidazole, linezolid, and clarithromycin, are responsible for the majority of these interactions^[11]. In addition, advanced age and a greater total number of medications have been identified as independent risk factors for the development of pDDIs^[12].

In light of these findings, determining the prevalence and predictors of antimicrobial-related pDDIs in hospitalized patients is important for developing strategies to improve patient safety. In this study, the point prevalence and clinical determinants of antimicrobial-related pDDIs were evaluated among hospitalized adult patients. In addition, the distribution of risk categories and the most frequently implicated agents were systematically analyzed.

Materials and Methods

Study Design and Patient Selection

This study used a cross-sectional point prevalence design and was conducted on March 4, 2026, at Şişli Hamidiye Etfal Training and Research Hospital to evaluate antimicrobial-related pDDIs. Adult patients aged 18 years or older who were hospitalized on the study date and were receiving at least 1 systemic antimicrobial agent and at least 1 additional systemic medication were included. Topical, ophthalmic, and intranasal medications were excluded from the evaluation.

Data Collection

Patient data were collected by the investigators from the hospital information management system and medical records. Demographic characteristics (age and sex), hospitalization ward, and all systemic medications and antimicrobials administered on the study date were recorded. Polypharmacy was defined as the concomitant use of 5 or more systemic medications.

Identification of pDDIs

All concomitantly administered medications were analyzed using the UpToDate® Lexicomp® Drug Interactions Online Database. Lexicomp was selected because it is a widely used and regularly updated clinical decision support database that provides comprehensive information on DDIs and is commonly used in clinical practice and research. The database classifies pDDIs into 5 risk categories: A (no known interaction), B (no action needed), C (monitor therapy), D (consider therapy modification), and X (avoid combination). In this study, interactions classified as categories C, D, and X were considered pDDIs. Interactions classified as categories D and X were considered clinically higher-risk interactions. Drug pairs associated with pDDIs and their potential clinical consequences were systematically recorded.

Ethics Approval

The study was approved by the University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee (decision number: 3409; date: March 3, 2026) and was conducted in accordance with the principles of the Declaration of Helsinki. Because anonymized data obtained from hospital records were used, the requirement for informed consent was waived by the ethics committee.

Statistical Analysis

Continuous variables were presented as mean $\pm$ standard deviation or median (interquartile range [IQR]), according to data distribution, whereas categorical variables were expressed as numbers and percentages. Between-group differences were evaluated using the Mann-Whitney U test for continuous variables and the Pearson chi-square test or Fisher exact test for categorical variables.

Univariable and multivariable logistic regression analyses were performed to identify independent risk factors associated with antimicrobial-related pDDIs. Variables with $p < 0.20$ in the univariable analysis, as well as variables considered clinically relevant, were included as candidate variables in the multivariable model. A bidirectional stepwise selection method (forward and backward) based on the Akaike information criterion (AIC) was used to construct the final model. Because

of the structural relationship between the total number of medications and polypharmacy (defined as a binary variable based on the use of ≥ 5 medications), these 2 variables were not included simultaneously in the same model. The total number of medications was included in the final model because it retained the characteristics of a continuous variable and provided a better model fit. Multicollinearity was assessed using the variance inflation factor (VIF), and VIF values < 2 were confirmed for all variables. Model fit was evaluated using the AIC, likelihood ratio (LR) chi-square test, and Hosmer-Lemeshow goodness-of-fit test. A p value < 0.05 was considered statistically significant. All analyses were performed using R statistical software (version 4.5.0; R Foundation for Statistical Computing, Vienna, Austria) and the gtsummary package.

Results

Patient Characteristics

At the time of the study, a total of 719 patients were hospitalized, excluding those in pediatric wards. After excluding patients who were not receiving antimicrobials and those receiving antimicrobial therapy without concomitant medications, 375 patients (52.2%) met the inclusion criteria and were included in the study. The median age was 65 years (IQR, 49-77 years), and 202 patients (53.9%) were male. Of the included patients, 70 (18.7%) were hospitalized in the intensive care unit, 127 (33.9%) in medical wards, and 178 (47.5%) in surgical wards. The median length of hospital stay was 4 days (IQR, 1-9 days).

A total of 350 patients (93.3%) were receiving 3 or more medications, 253 (67.5%) were receiving 5 or more medications, and 82 (21.9%) were receiving 10 or more medications. The median total number of medications per patient was 6 (IQR, 4-7). Regarding antimicrobial use, 259 patients (69.1%) received 1 antimicrobial agent, 100 (26.7%) received 2, and 16 (4.3%) received 3 or more antimicrobial agents. The median number of antimicrobials per patient was 1 (IQR, 1-1).

The median total number of medications was 9 (IQR, 7-12) among patients hospitalized in the intensive care unit, compared with 5 (IQR, 4-8) among those hospitalized in other wards ($p < 0.001$). Similarly, the median number of antimicrobials was 2 (IQR, 1-2) among intensive care unit patients and 1 (IQR, 1-2) among patients hospitalized in other wards ($p < 0.001$).

Prevalence and Distribution of pDDIs

A total of 205 antimicrobial-related pDDI pairs were identified. At least 1 pDDI was present in 112 patients (29.9%). When interactions were evaluated according to risk category, 5% ($n = 10$) were classified as category X, 27% ($n = 55$) as category D, and 68% ($n = 140$) as category C.

When all risk categories were considered, the most frequently implicated agents in pDDIs were ceftriaxone (n=44), clarithromycin (n=33), and levofloxacin (n=18), followed by cefuroxime axetil (n=17) and moxifloxacin (n=15).

When clinically higher-risk category D and X interactions were considered together, the most frequently implicated agents were clarithromycin (n=18), cefuroxime axetil (n=17), and linezolid (n=9) (Table 1; Figure 1).

Patients with pDDIs were older and had longer hospital stays and a greater number of medications and antimicrobials used than patients without pDDIs ($p<0.001$ for all comparisons). In addition, the proportions of patients hospitalized in the intensive care unit and those with polypharmacy were significantly higher among patients with pDDIs ($p=0.041$ and $p<0.001$, respectively) (Table 2).

Identification of Independent Risk Factors for pDDIs: Multivariable Logistic Regression Analysis

In the univariable analysis, age [odds ratio (OR), 1.02; 95% confidence interval (CI), 1.01-1.03; $p<0.001$], female sex (OR, 0.60; 95% CI, 0.38-0.95; $p=0.029$), intensive care unit hospitalization (OR, 1.75; 95% CI, 1.02-3.00; $p=0.041$), total number of medications (OR, 1.39; 95% CI, 1.29-1.51; $p<0.001$), number of antimicrobials (OR, 2.45; 95% CI, 1.69-3.61; $p<0.001$), and presence of polypharmacy (OR, 8.76; 95% CI, 4.47-19.3; $p<0.001$) were significantly associated with pDDIs. In the multivariable model, the total number of medications (OR, 1.40; 95% CI, 1.28-1.54; $p<0.001$) and female sex (OR, 0.57; 95% CI, 0.33-0.95; $p=0.034$) were identified as independent predictors. Intensive care unit hospitalization showed an inverse association in the multivariable model (OR, 0.50; 95% CI, 0.25-0.98; $p=0.049$). Age and number of antimicrobials were no longer statistically significant in the multivariable model. The results of the univariable and multivariable logistic regression analyses are presented in Table 3.

In the goodness-of-fit analyses, the Hosmer–Lemeshow test showed no significant discrepancy between the model and the observed data ($p>0.05$). The LR chi-square test demonstrated that the model provided a significantly better fit than the null model ($p<0.001$). The Nagelkerke R^2 value supported the explanatory power of the model.

Discussion

In this study, at least 1 antimicrobial-related pDDI was identified in 29.9% of hospitalized adult patients receiving systemic antimicrobial therapy. Nearly one-third of these interactions were classified as category D or X, suggesting that they may have clinically important implications and warrant careful attention from a patient safety perspective. Furthermore, the

finding that the total number of medications was the strongest independent predictor of pDDIs in the multivariable analysis highlights the important role of overall medication burden in the occurrence of these interactions.

The 29.9% prevalence of pDDIs identified in our study appears to be lower than the rates reported in studies evaluating drug interactions more broadly, likely because our analysis was limited to antimicrobial-related interactions. Indeed, studies investigating drug interactions at the hospital level have reported substantially higher prevalence rates. A multicenter prospective study conducted in Norway identified at least 1 drug-related problem in 81% of patients^[13], whereas studies evaluating all drug interactions in medical intensive care units reported prevalence rates as high as 46.3%^[14]. In contrast, lower rates have been reported in studies focusing specifically on antimicrobial-related interactions. In one study evaluating interactions between antimicrobials and other medications, the prevalence of pDDIs was 21.4%^[15], whereas a multicenter point prevalence study conducted in Türkiye reported a prevalence of 22.7%^[11]. However, prevalence rates appear to increase in specific patient populations with a high medication burden. The proportion of patients with at least 1 pDDI has been reported to reach 88% among intensive care unit patients receiving antimicrobials^[16], while a prevalence of 42% was reported in a geriatric population^[12]. Taken together, these findings suggest that the prevalence of pDDIs varies not only according to the scope of the analysis but also according to patient characteristics and, particularly, the burden of polypharmacy. Although the prevalence observed in our study was lower than that reported in broader analyses, its similarity to findings from antimicrobial-focused studies supports the potential influence of patient characteristics and medication burden on the occurrence of pDDIs.

The identification of the total number of medications as an independent predictor of pDDIs in the multivariable analysis suggests that the effects of factors such as age, number of antimicrobials, and intensive care unit hospitalization, which were significant in the univariable analysis, may be partly explained by their relationship with overall medication burden. The literature similarly identifies the number of medications as one of the strongest and most consistent predictors of DDIs^[17,18]. Indeed, some variables, such as advanced age, have been shown to lose much of their independent predictive value after adjustment for the number of medications. Nevertheless, some studies have reported that advanced age and intensive care unit hospitalization remain independent risk factors regardless of medication count, and these discrepancies may be attributable to differences in patient populations, clinical settings, and analytical methods^[15,19].

Table 1. Clinically higher-risk antimicrobial-related pDDIs (Categories D and X): Interaction mechanisms and potential clinical consequences.

Antimicrobial	Interacting drug	n	Risk rating	Interaction mechanism/clinical consequences
Clarithromycin	Papaverine hydrochloride	1	X	Pharmacodynamic additive effect; QT prolongation and torsades de pointes risk
	Nimodipine	1	X	CYP3A4 inhibition; increased drug exposure and hypotension risk
	Quetiapine	1	X	CYP3A4 inhibition; QT prolongation risk
	Amiodarone	1	X	Pharmacodynamic additive QT effect; QT prolongation and torsades de pointes risk
	Sildenafil	1	X	CYP3A4 inhibition; increased drug exposure and hypotension risk
	Lercanidipine	2	X	CYP3A4 inhibition; increased drug exposure and hypotension risk
	Tamsulosin	1	X	CYP3A4 inhibition; increased tamsulosin exposure and hypotension risk
	Budesonide	5	D	CYP3A4 inhibition; increased systemic corticosteroid exposure and adrenal suppression risk
	Atorvastatin	4	D	CYP3A4/SLC01B1 inhibition; increased atorvastatin exposure and rhabdomyolysis/myopathy risk
	Tolterodine	1	D	CYP3A4 inhibition (CYP2D6-poor metabolizers); increased drug exposure and anticholinergic toxicity risk
Cefuroxime axetil	Proton pump inhibitors	17	D	Increased gastric pH resulting in reduced absorption; decreased antibiotic efficacy
Ceftriaxone	Calcium salts	3	D	Precipitation with calcium; risk of vascular precipitate formation
Meropenem	Valproic acid	1	D	Reduced valproate enterohepatic recirculation; subtherapeutic valproic acid levels and seizure risk
Ciprofloxacin	Clozapine	1	D	CYP1A2 inhibition and additive QT effect; increased clozapine levels and QT prolongation risk
Levofloxacin	Quetiapine	3	D	Additive QT-prolonging effect; QT interval prolongation and torsades de pointes risk
Daptomycin	Statins	5	D	Additive skeletal muscle toxicity; myopathy and rhabdomyolysis risk
Metronidazole	Diazepam	1	X	Ethanol-acetaldehyde accumulation; disulfiram-like reaction
Linezolid	Tramadol	1	X	Linezolid MAOI-like activity with a serotonergic opioid; serotonin syndrome risk
	Remifentanyl	5	D	Linezolid MAOI-like activity; serotonin syndrome and opioid toxicity (respiratory depression) risk
	Sympathomimetics	3	D	Linezolid MAOI-like activity; hypertensive crisis risk
Moxifloxacin	Iron preparations	1	D	Chelation forming an insoluble complex; reduced absorption and decreased antibiotic efficacy
	Magnesium salts	2	D	Chelation with insoluble complex formation; reduced antibiotic absorption
Fluconazole	Clopidogrel	1	D	CYP2C19 inhibition; reduced clopidogrel active metabolite and diminished antiplatelet effect
	Quetiapine	1	D	CYP3A4 inhibition and additive QT effect; increased quetiapine exposure and QT prolongation risk
Posaconazole	Proton pump inhibitors	1	D	Increased gastric pH, reducing absorption; decreased posaconazole exposure and risk of prophylaxis failure
Voriconazole	Trazodone	1	D	CYP3A4 inhibition; increased trazodone exposure, sedation, and QT prolongation risk

pDDI, potential drug-drug interaction; CYP, cytochrome P450; CYP1A2, cytochrome P450 1A2; CYP2C19, cytochrome P450 2C19; CYP2D6, cytochrome P450 2D6; CYP3A4, cytochrome P450 3A4; D, therapy modification recommended; MAOI, monoamine oxidase inhibitor; n, number of identified interactions; QT, QT interval; SLC01B1, solute carrier organic anion transporter family member 1B1; X, avoid combination.

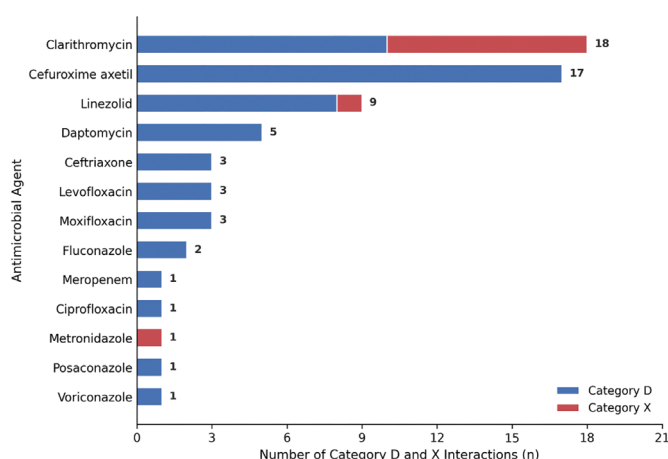


Figure 1. Distribution of clinically higher-risk (categories D and X) antimicrobial-related pDDIs according to antimicrobial agent. Blue bars represent category D interactions (therapy modification recommended), whereas red bars represent category X interactions (avoid combination). pDDIs, potential drug-drug interactions.

In our study, each 1-unit increase in the total number of medications was associated with approximately 1.40-fold higher odds of pDDIs, indicating a cumulative increase in interaction risk. This finding is consistent with the literature^[20] and supports prioritizing systematic interaction screening, particularly among patients receiving multiple medications.

The finding that female sex was associated with lower odds of pDDIs in the multivariable analysis is noteworthy. The relationship between sex and the risk of DDIs remains unclear in the literature. While some studies have reported a higher risk of DDIs among women, others have found no significant association^[21]. In our study, this finding may be related to sex-specific differences in comorbidity distribution,

prescribing patterns, or clinical presentation. However, given the observational design of the study, this association should not be interpreted as causal.

The finding that intensive care unit hospitalization was positively associated with pDDIs in the univariable analysis but inversely associated with pDDIs in the multivariable model may initially appear counterintuitive. Patients admitted to the intensive care unit had a higher medication burden, and the total number of medications was the strongest independent predictor of pDDIs. Therefore, adjustment for medication burden may have attenuated the independent contribution of intensive care unit hospitalization and contributed to the reversal in the direction of the association. Marked multicollinearity is unlikely to explain this finding, as the VIF values were below 2 for all variables included in the model. Accordingly, the adjusted association should not be interpreted as evidence of a true protective effect, and residual confounding may also have contributed to this finding.

In our study, the majority of antimicrobial-related pDDIs were classified as category C (68%), followed by categories D (27%) and X (5%). This distribution is consistent with previous reports showing that most interactions fall within category C^[22,23]. Nevertheless, the finding that category D and X interactions together accounted for 32% of all identified pDDI pairs is clinically important. Previous studies have reported rates ranging from 8% to 32% for category D interactions and from 1% to 13% for category X interactions^[24-27]. The relatively high proportion of category D interactions observed in our study may be related to the heterogeneous nature of the study population, high medication burden, and widespread antimicrobial use. Although the proportion of category X interactions in our study (5%) appears consistent with previously reported rates, their

Table 2. Comparison of patients with and without pDDIs.

Variable	Patients without pDDIs (n = 263)	Patients with pDDIs (n = 112)	p value
Age, years	62 (46-76)	71 (55.8-80)	<0.001
Sex			0.029
Male	132 (50.2)	70 (62.5)	
Female	131 (49.8)	42 (37.5)	
Ward type			0.041
General ward	221 (84.0)	84 (75.0)	
Intensive care unit	42 (16.0)	28 (25.0)	
Length of hospital stay, days	4 (1-7)	6 (3-12.3)	<0.001
Total number of medications	5 (4-7)	9.5 (7-12)	<0.001
Number of antimicrobials	1 (1-1)	1 (1-2)	<0.001
Polypharmacy			<0.001
No	114 (43.3)	9 (8.0)	
Yes	149 (56.6)	103 (92.0)	

Data are presented as median (IQR) or n (%). IQR, interquartile range; pDDI, potential drug-drug interaction.

Table 3. Univariable and multivariable logistic regression analyses of factors associated with the development of pDDIs.

	Univariable		Multivariable	
Characteristics	OR (95% CI)	p value	OR (95% CI)	p value
Age (per 1-year increase)	1.02 (1.01-1.03)	<0.001	1.00 (0.99-1.02)	0.601
Sex				
Male	Reference	—	Reference	—
Female	0.60 (0.38–0.95)	0.029	0.57 (0.33-0.95)	0.034
Ward type				
General ward	Reference	—	Reference	—
Intensive care unit	1.75 (1.02-3.00)	0.041	0.50 (0.25-0.98)	0.049
Length of hospital stay (per 1-day increase)	1.02 (1.00-1.04)	0.078	—	—
Total number of medications	1.39 (1.29-1.51)	<0.001	1.40 (1.28-1.54)	<0.001
Number of antimicrobials	2.45 (1.69-3.61)	<0.001	1.36 (0.89-2.09)	0.156
Polypharmacy				
No	Reference	—	—	—
Yes	8.76 (4.47-19.3)	<0.001	—	—

CI, confidence interval; OR, odds ratio; pDDI, potential drug-drug interaction.

potential clinical importance should not be underestimated because these interactions represent contraindicated combinations. These findings support the need for systematic evaluation of DDIs, particularly when planning antimicrobial therapy for high-risk patients.

When all risk categories were considered, the highest numbers of interactions were associated with ceftriaxone (n=44), clarithromycin (n=33), and levofloxacin (n=18). This finding may be explained by the widespread clinical use of these agents. Although ceftriaxone was the most frequently implicated agent, most of the interactions involving ceftriaxone were classified as category C, suggesting that their clinical impact may be limited. This finding is consistent with studies demonstrating that electronic interaction databases may identify a large number of low-risk interactions and that only a proportion of reported interactions are associated with actual clinical consequences^[28].

Among the category D and X interactions, clarithromycin (n=18), cefuroxime axetil (n=17), and linezolid (n=9) were the most frequently implicated agents. The prominent contribution of clarithromycin is likely related to its potent CYP3A4 inhibitory effect, and its interaction potential, particularly with statins and other CYP3A4 substrates, has been well described in the literature^[29]. All interactions observed with cefuroxime axetil involved proton pump inhibitors, which is consistent with the pH-dependent absorption profile of this agent^[30]. Given the widespread use of proton pump inhibitors in hospitalized patients, this interaction may be encountered frequently in routine clinical practice. Therefore, when

prescribing cefuroxime axetil to patients receiving proton pump inhibitor therapy, clinicians should be aware of the potential for reduced drug absorption.

In addition, the finding that agents such as quinolones and linezolid were associated with higher-risk interaction categories despite their relatively lower frequency of use suggests that interaction risk does not necessarily parallel prescribing frequency. The interaction potential of quinolones through QT prolongation and cytochrome enzyme pathways, as well as the serotonergic interactions associated with linezolid through monoamine oxidase inhibition, may explain this finding^[31,32]. These findings support the need for systematic evaluation of not only causative microorganisms and resistance patterns but also concomitant medication use when planning antimicrobial therapy.

However, these findings should be interpreted in light of an important limitation of the present study. Because only pDDIs were evaluated, treatment modifications, drug discontinuation, and adverse drug events associated with these interactions could not be assessed. Nevertheless, identifying high-risk antimicrobial-related pDDIs may facilitate timely medication review, support appropriate treatment modifications when necessary, and help prevent potentially avoidable adverse drug events. Therefore, integrating routine pDDI screening into antimicrobial stewardship programs and daily clinical practice may contribute to safer prescribing and improved patient safety, particularly among patients receiving multiple concomitant medications.

Study Limitations

This study has several limitations. Its cross-sectional and single-center design precludes assessment of causal relationships. Furthermore, because data were collected at a single time point, the findings represent a snapshot of prescribing practices and antimicrobial-related pDDIs on the study day and may not fully reflect temporal changes in prescribing patterns. In addition, the study was limited to the identification of pDDIs and did not capture whether these interactions resulted in clinically relevant consequences, including treatment modification, discontinuation of therapy, or adverse drug events. Therefore, the actual clinical significance of the identified pDDIs could not be determined. Furthermore, although Lexicomp is a widely used and regularly updated clinical decision support database, pDDI assessment was performed using a single electronic database. Differences in the identification and risk classification of DDIs among available databases may therefore have influenced the results. Nevertheless, our study provides contemporary real-world data on the burden of antimicrobial-related pDDIs and associated risk factors in a large hospital population.

Conclusion

In conclusion, antimicrobial-related pDDIs were identified in 29.9% of hospitalized adult patients, with 32% of the identified interactions classified as category D or X. Clinically important category D and X interactions were predominantly associated with clarithromycin, cefuroxime axetil, linezolid, and quinolones, highlighting the need for careful evaluation of concomitant medications when these agents are prescribed. The total number of medications was the strongest independent predictor of pDDIs, underscoring the central role of medication burden in interaction risk. These findings support the importance of systematic DDI screening during antimicrobial therapy. Accordingly, integrating routine pDDI screening into hospital antimicrobial stewardship programs, supported by multidisciplinary medication review involving clinical pharmacists, may facilitate the early identification and management of clinically higher-risk interactions and contribute to safer antimicrobial prescribing and improved patient safety.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee (decision number: 3409; date: March 3, 2026) and was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Because anonymized data obtained from hospital records were used, the requirement for informed consent was waived by the ethics committee.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.D.D., H.M.T., Concept: N.D.D., H.M.T., Design: N.D.D., H.M.T., Data Collection or Processing: N.D.D., H.M.T., Analysis or Interpretation: O.D., Writing: N.D.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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