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Evaluation of Potential Drug-Drug Interactions Caused by Antibacterial and Antifungal Drugs in the Intensive Care Unit: A Retrospective Cross-Sectional Study

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ABSTRACT

Objective: Antimicrobial drugs are frequently used in the intensive care unit (ICU) and may cause drug-drug interactions (DDIs) which change treatment outcomes. This study aims to determine the frequency of potential DDIs (pDDIs) caused by antimicrobial drugs in the ICU, according to two databases, address the differences between these two databases, discuss the clinical significance of pDDIs and investigate their relationship with clinical outcomes.

Materials and Methods: This study was designed as a 1-year retrospective cross-sectional study. Patients over the age of 18 who used antimicrobials for at least 72 hours were included. pDDIs between other drugs and antimicrobials were checked using the "drug interactions" modules of the Lexicomp and Micromedex databases. Data were collected from the hospital's records by a clinical pharmacist.

Results: A total of 393 drug profiles were evaluated for 100 patients, of which 84.2% were antibacterial drugs. According to at least one database, 88% of patients had pDDIs. Of these, 62.4% were classified as major according to at least one database. Only 27.3% of pDDIs had the same level of interaction in both databases. Common pDDIs posed risks such as additive nephrotoxicity, excessive sedation, respiratory depression and QT interval prolongation.

Conclusion: pDDIs should be checked not only by one database but by multiple databases, coupled with the input of an experienced clinical pharmacist.

Keywords: Antibacterial drug, antifungal drug, drug-drug interactions, intensive care, clinical pharmacy.

INTRODUCTION

A drug-drug interaction (DDI) is defined as a pharmacological or clinical response to the administration of two or more drugs that differs from the response observed when the drugs are administered individually.[1] As a result of DDIs, there can be a decrease in drug efficacy or an increase in toxicity, potentially

leading to therapeutic failure or life-threatening adverse drug reactions (ADRs). In the intensive care unit (ICU), DDIs are associated with increased lengths of hospital stay and costs.[1] When detected, DDIs are theoretically evaluated through databases and considered potential, not necessarily indicating actual occurrence.[2] We will use the term potential DDI (pDDI) throughout this manuscript to describe drug-drug interactions identified by databases.

There is general consensus in the literature that polypharmacy contributes to DDIs.[2,3] Critically ill patients are at an increased risk of DDIs due to the large number of medications they require for their complex clinical conditions.[4,5] A significant group of drugs contributing to polypharmacy in ICUs is antimicrobial drugs which are often used for treating infections.[6] Given the effects of antibacterial and antifungal drugs on the cytochrome P450 enzyme system (CYP) and their potential to prolong the QT interval, these drugs may cause DDIs. Among the DDIs commonly studied in ICUs, those caused by antimicrobial drugs are less frequent. However, the frequency of a DDI does not necessarily correlate with its clinical significance.[7] Therefore, to specifically focus on DDIs that may be caused by antimicrobial drugs, our study exclusively investigated these interactions.

Numerous studies compare drug interaction databases to assess their effectiveness in detecting clinically significant DDIs.[8,9] In a systematic review analyzing these studies, Micromedex and Lexicomp, which we used in our study, were identified as the most reliable drug interaction databases.[9] Consequently, we employed these databases to detect pDDIs and clinically significant pDDIs in our study. Additionally, our study explored how these detected pDDIs should be managed.

This study aimed to determine the frequency of pDDIs caused by antimicrobial drugs in the ICU, using two databases. Our objectives were to address the differences between these two databases, discuss the clinical significance of the pDDIs, and investigate their association with clinical outcomes, such as the length of ICU stay, Acute Physiology And Chronic Health Evaluation II (APACHE II) scores, and Sequential Organ Failure Assessment (SOFA) scores on days 1, 7, and 14.

MATERIALS AND METHODS

Study Design and Setting

In this retrospective cross-sectional study, we analyzed the medical records of patients in the ICU of the Internal Diseases Department at Erciyes University, Faculty of Medicine, spanning from January 1, 2019, to December 31, 2019. Data collection was conducted between July 1 and July 31, 2020.

Ethical Considerations

This study was approved by the Erciyes University Clinical Research Ethics Committee (date: June 24, 2020; no: 2020/324). To access the data of patients within the scope of the study, approval was obtained from the Chief Physician of Erciyes University Hospitals.

Data Collection

Patients aged 18 and over who used antibacterial and/or antifungal drugs for at least 72 hours were included in our study. This inclusion criterion was based on the assumption that most drugs reach steady-state concentration within this timeframe. Pregnant and breastfeeding patients, as well as patients using antimicrobial drugs solely for prophylactic purposes, were excluded.

We recorded the patients' demographic information, comorbidities, diagnosis upon hospitalization, place of admission to the ICU, vital signs, and APACHE II score on the first day of hospitalization, along with SOFA scores on days 1, 7, and 14 of hospitalization. All drugs used by patients and laboratory findings within the first 14 days from the hospitalization date were recorded. Mechanical ventilation, renal function replacement, and vasoactive drug use were documented by examining all days of hospitalization. The length of ICU stay and mortality status of the patients were also recorded. Patient data were collected from the "Intensive Care Observation Form" and the hospital's medical records by a clinical pharmacist.

Identifying Potential Drug-Drug Interactions

Potential drug-drug interactions between the antibacterial and antifungal drugs used by patients and other drugs were checked by a clinical pharmacist according to the Lexicomp and Micromedex databases (as of March 2021).[10,11]

According to the Micromedex database, pDDIs are divided into four categories:

1. Contraindicated: Concurrent use is contraindicated.
2. Major: Concurrent use may be life-threatening, or a serious intervention may be needed due to reported adverse reactions.
3. Moderate: Concurrent use can worsen the patient's medical condition, or alternative therapy may be required.
4. Minor: Concurrent use results in low adverse effects that do not necessitate any alteration in therapy.

According to the Lexicomp database, pDDIs are divided into five categories:

- X: Avoid combination.
- D: Consider therapy modification.
- C: Monitor therapy.
- B: No action needed.
- A: No known interaction.

Interaction levels that do not require intervention were not included in the interaction assessment. Categories A and B from the Lexicomp database, and the Minor category from the Micromedex database, were excluded. A clinically significant pDDI was defined as an interaction corresponding with a Major or Contraindicated rating in both databases.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 18.0 (IBM SPSS Statistics for Windows, Version 18.0; IBM Corp., Armonk, NY, USA). Quantitative data were expressed as mean±standard deviation (SD) or median and interquartile range (Q_1–Q_3), depending on their distribution. Qualitative data were presented as numbers and percentages. Age, body weight, SOFA score on day 1, length of ICU stay, and the duration of invasive mechanical ventilation (IMV), non-invasive mechanical ventilation (NIMV), hemodialysis (HD), and vasopressor use were not normally distributed and thus were presented as median and interquartile range (Q_1–Q_3). The correlation among the number of drugs, pDDIs, APACHE II score, and SOFA scores on days 1, 7, and 14, along with the length of ICU stay, was evaluated using Spearman's correlation analysis. Statistical significance was set at a p-value of <0.05.

RESULTS

Demographic and Clinical Characteristics of the Patients

The characteristics of the 100 patients included in the study are presented in Table 1. The median age of the patients was 62.5 years (range: 50–72) and 51% (n=51) were female. Of the patients included in the study, 82% were hospitalized from clinical services, 10% from an external hospital and 8% from the emergency room to the ICU.

Respiratory failure (53%) and sepsis/septic shock (15%) were the most common causes of admission to the ICU. The most common comorbidities among the patients were malignancy (56%), cardiovascular system diseases (41%) and hypertension (34%).

The median body weight was 80 kg (range: 60–80). The mean APACHE II score was 21.9±7.63. The median SOFA scores were 9.0 (range: 6.0–13.0) on day 1, 10.0±4.37 on day 7, and 10.1±4.29 on day 14. The median length of ICU stay was 11.5 days (range: 6.0–19.0).

Of the patients, 91 (91%) received IMV, 36 (36%) NIMV and 29 (29%) received both IMV and NIMV support. The median number of days for IMV support was 8.0 (range: 4.0–16.0), and the NMIV support was 3.0 days (range: 2.0–7.0). Forty-six (46%) patients underwent hemodialysis (HD), 14 (14%) received continuous renal replacement therapy (CRRT) and 8 (8%) received both HD and CRRT. The median number of days on HD was 3.0

Table 1. Demographic and clinical characteristics of the patients

Variable	Variable patients (n=100)
Age (years), median (Q_1–Q_3)	62.5 (50.0–72.0)
Sex, n (%)	
Male	49 (49%)
Female	51 (51%)
Body weight (kg), median (Q_1–Q_3)	80.0 (60.0–80.0)
APACHE II score, mean±SD	21.9±7.63
SOFA score	
Day 1 (n=100), median (Q_1–Q_3)	9.0 (6.0–13.0)
Day 7 (n=71), mean±SD	10.0±4.37
Day 14 (n=47), mean±SD	10.1±4.29
Admission reasons	
Respiratory reasons	53 (53%)
Sepsis/septic shock	15 (15%)
Surgical reasons	9 (9%)
Gastrointestinal reasons	6 (6%)
Metabolic reasons	5 (5%)
Neurological reasons	5 (5%)
Other reasons	7 (7%)
Comorbidity, n (%)	
Malignancy	56 (56%)
Cardiovascular system disease	41 (41%)
Hypertension	34 (34%)
Diabetes mellitus	24 (24%)
Asthma/COPD	22 (22%)
Chronic kidney disease	20 (20%)
Chronic liver disease	10 (10%)
Renal dysfunction, n (%)	58 (58%)
Liver enzyme elevation, n (%)	17 (17%)
ICU stay (days), median (Q_1–Q_3)	11.5 (6.0–19.0)
MV support, n (%)	
IMV	91 (91%)
NIMV	36 (36%)
Both IMV/NIMV	29 (29%)
IMV duration (days), median (Q_1–Q_3)	8.0 (4.0–16.0)
NIMV duration (days), median (Q_1–Q_3)	3.0 (2.0–7.0)
Renal support, n (%)	
HD	46 (46%)
CRRT	14 (14%)
Both HD/CRRT	8 (8%)
HD duration (days), median (Q_1–Q_3)	3.0 (2.0–5.0)
CRRT duration (days), mean±SD	3.4±2.10
Vasopressor support	91 (91%)
Vasopressor duration (days), median (Q_1–Q_3)	5.0 (3.0–9.0)

SD: Standard deviation; Q: Quartile; APACHE: Acute physiology and chronic health evaluation; SOFA: Sequential organ failure assessment; COPD: Chronic obstructive pulmonary disease; ICU: Intensive care unit; MV: Mechanical ventilation; IMV: Invasive mechanical ventilation; NIMV: Non-invasive mechanical ventilation; HD: Hemodialysis; CRRT: Continuous renal replacement therapy.

Table 2. Evaluated antibacterial and antifungal drugs

Evaluated drugs	n	%
Antibacterial	331	84.2
Antifungal	62	15.8
Antibacterial		
Meropenem	73	18.6
Vancomycin	70	17.8
Colistin	52	13.2
Co-trimoxazole	31	7.9
Piperacillin/Tazobactam	25	6.4
Clarithromycin	15	3.8
Others	65	16.5
Antifungal		
Amphotericin B	22	5.6
Azoles	21	5.3
Echinocandins	19	4.8

Table 3. Information on drug interaction

	n	%
Interaction presence by databases		
Lexicomp and/or Micromedex	74	74
Only Lexicomp	13	13
Only Micromedex	1	1
No interaction	12	12
Interactions according to Lexicomp database	355	
Level X	6	1.7
Level D	145	40.8
Level C	204	57.5
Interactions according to Micromedex database	269	
Contraindicated	5	1.8
Major	185	68.8
Moderate	79	29.4

(range: 3.0–5.0) and the mean duration of CRRT was 3.4±2.10 days. Ninety-one (91%) of the patients received vasopressor therapy, with the median number treatment duration being 5.0 days (range: 3.0–9.0).

Details of Antibacterial and Antifungal Drugs Evaluated

A total of 393 antimicrobial drugs were evaluated for the 100 patients included in the study. Of these drugs, 331 (84.2%) were antibacterial and 62 (15.8%) were antifungal drugs. The most commonly used drugs were meropenem (18.6%), vancomycin (17.8%) and colistin (13.2%). The drugs evaluated are listed in Table 2.

Identified Potential Drug-Drug Interactions

The median number of drugs administered to patients was 12 (range: 7–18). 88% of patients were exposed to pDDIs caused by antibacterial/antifungal drugs, according to at least one database. The number of pDDIs per patient was 2.0 (range: 1.0–5.0) according to Lexicomp and 2.0 (range: 0.2–4.7) according to Micromedex [median (interquartile interval)].

74% of the patients had at least one pDDI according to both Lexicomp and Micromedex, 13% with Lexicomp only, 1% with Micromedex only and 12% with no known pDDI in either database.

A total of 355 pDDIs were identified according to the Lexicomp database. 1.7% of them (6) were level X (avoid concomitant use), 40.8% of them (145) were level D (consider adjusting therapy), and 57.5% of them (204) were detected as level C (follow therapy). According to the Micromedex database, a total of 269 pDDIs were detected. 1.8% of them (5) were contraindicated, 68.8% of them (185) were major and 29.4% of them (79) were moderate. pDDI data are presented in Table 3.

When combining the pDDIs detected in both databases, there were 410 pDDIs, of which 148 were from different drug pairs. 62.4% (256/410) of pDDIs were classified as major according to at least one database. The agreement between Lexicomp and Micromedex databases was 21.6% (32/148).

The most common pDDIs were determined between the following three drug pairs according to the Lexicomp database: colistin and vancomycin, amphotericin B and antihypertensive drugs, azole antifungal drugs and fentanyl. According to the Micromedex database, the most common pDDIs were between azole antifungal drugs and fentanyl, quinolones and corticosteroids, piperacillin/tazobactam and vancomycin. The ten most common pDDIs identified by at least one database and their potential effects are presented in Table 4. The drug pair found to be contraindicated in both databases was voriconazole-rifampicin. Drug pairs that are contraindicated according to Lexicomp and Micromedex databases are listed in Tables 4 and 6. 18.0% of the detected pDDIs were clinically significant; these are presented in Table 5.

As the number of drugs used increases, so does the number of pDDIs, according to both Lexicomp (rho: 0.574; $p<0.001$) and Micromedex (rho: 0.434; $p<0.001$) databases. No statistically significant correlation was found between the number of pDDIs (according to both Lexicomp and Micromedex) and the length of ICU stay, APACHE II score, or SOFA scores on days 1, 7, and 14. Statistical data are presented in Table 6.

Table 4. The ten most common pDDIs pairs and remaining pDDIs

Drug pair	Total number	Potential impact	LXC	MM
Colistin-vancomycin	37	Risk of nephrotoxicity	D	-
Amphotericin B-antihypertensives	25	Risk of hypotension	C	-
Azoles-fentanyl	23	Increased serum concentration of fentanyl	D	Major
Quinolones-steroids	17	Increased risk of tendinitis	C	Major
Amphotericin B-steroids	15	Increased risk of hypokalemia	C	-
Amphotericin B-colistin	13	Increased risk of nephrotoxicity	D	-
Piperacillin/tazobactam-vancomycin	12	Increased risk of nephrotoxicity	C	Major
Fluconazole-pantoprazole	12	Pantoprazole serum concentration increased	-	Moderate
Voriconazole -pantoprazole	11	Pantoprazole serum concentration increased	C	Moderate
Clarithromycin-fentanyl	10	Increased serum concentration of fentanyl	D	Major

pDDIs: Potential drug-drug interactions; LXC: Lexicomp; MM: Micromedex.

DISCUSSION

Patients in the ICU are at high risk for DDIs due to the large number of drugs prescribed and the complexity of drug regimens.[12] The more drugs that are prescribed, the higher the risk of DDI.[14] In our study, the median number of drugs administered to patients was 12 (range: min 7, max 18). As the number of drugs used in patients increased, so did the number of pDDIs per patient, according to both the Lexicomp (rho: 0.574; p<0.001) and Micromedex (rho: 0.434; p<0.001) databases.

A meta-analysis examining the harmful effects of DDIs in hospitalized patients found that 67% of ICU patients were exposed to at least one pDDI.[2] Another meta-analysis evaluating pDDIs in ICU patients determined that 58% of the patients admitted to the ICU were exposed to at least one pDDI.[7] In our study, 88% of patients were exposed to pDDIs, according to at least one database. This rate may appear relatively higher because we excluded patients who did not use antimicrobial drugs in the ICU from our study.

In our study, a total of 410 pDDIs were detected between antimicrobial drugs and other drugs according to at least one database, with 148 of them consisting of different drug pairs. 62.4% (256/410) of pDDIs were classified as major by at least one of the databases. The agreement between the Lexicomp and Micromedex databases was 21.6%. In a study evaluating pDDIs in the medical ICU according to the Lexicomp and Micromedex databases, the rate of interaction at the major level was 24.9% (114/457) when compared to at least one database and the agreement between both databases was 18.9%.[12] In our study, the interaction agreement according to both databases was similar to that in Smithburger's study, but the rate of interaction at the major level was found to be higher. This difference may be attributed to our study's exclusive focus on the pDDIs of antimicrobial drugs and the smaller number of patients.

The number of pDDIs identified as contraindicated according to at least one database was nine, and there was one pDDI contraindicated in both databases. The remaining pDDIs (8) were classified by one of the databases as major (5), moderate (2), or minor (1). The pDDI between voriconazole and rifampicin is contraindicated in both databases. In a study with healthy volunteers, rifampicin was shown to reduce the bioavailability of voriconazole by 96%. Consequently, the concomitant use of voriconazole with strong CYP3A4 inducers like rifampicin is stated as contraindicated in the manufacturer's information.[14] If these two drugs are used together, and the infectious agent is Aspergillus sp., amphotericin B treatment may be considered instead of voriconazole. For other pathogens, alternative antifungals can be considered depending on the patient's clinical condition. It is crucial to avoid the concurrent use of these drugs in ICUs and to increase healthcare professionals' awareness of this issue.

According to database severity assessments, clinically significant pDDIs accounted for 18.0% (74/410) of all pDDIs. The most common clinically significant pDDIs involved azole antifungals and clarithromycin, which are strong CYP3A4 inhibitors, interacting with fentanyl, a CYP3A4 substrate. These interactions accounted for 41.9% (31/74) of cases. This pDDI might prolong the effects of fentanyl. Given the frequent use of fentanyl in mechanically ventilated patients, weaning may be delayed due to central nervous system depression. Close monitoring of patients is essential and this pDDI should be considered, particularly in patients with a history of prolonged ventilation. A dose reduction for fentanyl is recommended in

Table 5. Clinically significant pDDIs

Drug pair	Total number	Potential impact	LXC	MM
Clarithromycin-fentanyl	10	Increased serum concentration of fentanyl	D	Major
Azoles-fentanyl	23	Increased serum concentration of fentanyl	D	Major
Clarithromycin-midazolam	7	Increased serum concentration of midazolam	D	Major
Posaconazole-midazolam	6	Increased serum concentration of midazolam	D	Major
Linezolid-norepinephrine	4	Increased hypertensive effect	D	Major
Meropenem-valproic acid	3	Decreased serum concentration of Valproic acid	D	Major
Clarithromycin-diltiazem	3	Increased serum concentration of diltiazem	D	Major
Linezolid-fentanyl	3	Increased serotonergic effect	D	Major
Colistin-rocuronium	3	Increased neuromuscular-blocking effect	D	Major
Clarithromycin-amiodarone	2	Increased QT-prolonging effect	X	Major
Amikacin-colistin	2	Increased risk of nephrotoxicity	D	Major
Caspofungin-cyclosporine	2	Increased serum concentration of caspofungin	D	Major
Voriconazole-rifampicin	1	Decreased serum concentration of Voriconazole	X	Contraindicated
Levofloxacin-amiodarone	1	Increased QT-prolonging effect	X	Major
Linezolid-metoclopramide	1	Increased hypertensive effect	X	Major
Fluconazole-amiodarone	1	Increased QT-prolonging effect	D	Contraindicated
Linezolid-dobutamine	1	Increased hypertensive effect	D	Contraindicated
Fluconazole-clopidogrel	1	Decreased serum concentrations of the active metabolite(s) of clopidogrel	D	Major
Clarithromycin-rivaroxaban	1	Increased serum concentration of rivaroxaban	D	Major
Clarithromycin-quetiapine	1	Increased serum concentration of quetiapine and QT-prolonging effect	D	Major
Posaconazole-ruxolitinib	1	Increased serum concentration of ruxolitinib	D	Major
Voriconazole-solifenacin	1	Increased serum concentration of solifenacin	D	Major

pDDIs: Potential drug-drug interactions; LXC: Lexicomp; MM: Micromedex.

such cases. Another clinically significant pDDI was between midazolam and strong CYP3A4 inhibitors, occurring in 14.9% (11/74) of cases. This interaction may result in prolonged sedation due to increased serum concentration of midazolam. Reis & Cassiani[8] found that 15.5% (21/135) of adverse drug events in the ICU resulted from DDIs. They noted that in 42.9% of adverse drug reactions due to DDI, excessive sedation was observed in patients as a result of the interactions between midazolam and fentanyl and strong CYP3A4 inhibitors such as fluconazole and clarithromycin.[8] When midazolam and fentanyl are used concurrently with strong CYP3A4 inhibitors, lower initial doses may be prescribed, with gradual increases according to the patient's response. Another important consideration is that after discontinuing strong CYP3A4 inhibitors, the dose of midazolam or fentanyl may need to be increased again, depending on the clinical condition of the patient. Close patient monitoring is crucial in terms of analgosedation. Given the frequent use of these drugs in the ICU, healthcare professionals should be increasingly aware of this pDDI and exercise heightened caution.

Inconsistencies were observed between the two databases when evaluating pDDIs considered as major level. A total of 256 pDDIs are at the major level by at least one of the databases, of which 88 involve different drug pairs. Of these, 26.1% (23/88) of major pDDIs were identified in the Lexicomp database but not in the Micromedex database, and 12.5% (11/88) were identified in the Micromedex database and not in the Lexicomp database. While the colistin-vancomycin drug pair, determined as the most common pDDI, was listed in the ma-

Table 6. Correlation between pDDIs, number of drugs, and clinical outcomes

Clinical outcomes	Number of drugs		Number of pDDI (LXC)		Number of pDDI (MM)	
	ρ (rho)	p	ρ	p	ρ	p
Length of ICU stay	0.167	0.098	0.031	0.756	-0.042	0.680
APACHE II score	-0.040	0.696	-0.120	0.233	-0.110	0.280
SOFA score on day 1	0.080	0.428	-0.033	0.743	-0.136	0.181
SOFA score on day 7	0.318	0.007	0.029	0.809	-0.074	0.544
SOFA score on day 14	0.390	0.007	0.350	0.016	0.290	0.051

pDDIs: Potential drug-drug interactions; LXC: Lexicomp; MM: Micromedex; ICU: Intensive care unit; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment.

jor classification in the Lexicomp database, it was not defined in the Micromedex database. The concomitant use of these two agents can potentially increase nephrotoxicity. Although the Micromedex database has not defined this interaction, many studies in the literature show that the concomitant use of vancomycin and colistin increases nephrotoxicity.[15–18] In our study, 37 patients had this pDDI, and 23 (62.2%) of them experienced renal dysfunction. However, due to confounding factors such as the concomitant use of nephrotoxic agents and pre-existing renal dysfunction, it could not be clearly determined whether the renal dysfunction was directly related to the pDDI. The renal functions of patients using these two agents together should be closely monitored. If possible, instead of vancomycin, agents with gram-positive activity such as linezolid and daptomycin, which have lower nephrotoxicity potential, can be selected. The choice should consider the characteristics of the infection site and the resistance patterns of the pathogen. Linezolid is not preferred in catheter-related bloodstream infections, while daptomycin is not preferred in pneumonia.

The potential effect of 11.4% (47/410) of the pDDIs was the prolongation of the QT interval. Of these, 61.7% (29/47) are classified as major in the Micromedex database, while being unidentified or at the minor level in the Lexicomp database. The Lexicomp database classifies drugs according to the severity of their potential to prolong the QT interval. Therefore, the level of interaction varies according to the drug's potential to prolong the QT interval. On the other hand, the Micromedex database does not classify drugs based on the severity of their QT prolongation potential. As a result, the pDDI level is categorized as "major" in the use of any two drugs with QT prolongation potential in the Micromedex database.

It is important to note that detected pDDIs are not always clinically significant. In our study, clinically significant pDDIs constituted 18% of all pDDIs. The clinical significance of these pDDIs may depend on the concomitant medications and the patient's clinical features. In the current literature, there are few studies that demonstrate outcomes directly resulting from DDIs or that are causally associated with ADRs.[19–21] In a meta-analysis by Fitzmaurice et al.[7] evaluating DDIs in the ICU, it was determined that between 7% to 44% of ADRs were caused by DDIs. This wide range suggests that DDIs leading to ADRs should be further investigated. According to the study of Reis & Cassiani,[8] which examined ADRs in the ICU, antimicrobials rank second among drug groups causing adverse events. Considering the adverse events that occur due to DDIs, excessive sedation, hypotension, and acute kidney injury are the most common. In our study, the possible consequences of the most common pDDIs showed that additive nephrotoxicity of antimicrobials, excessive sedation, and QT interval prolongation were observed. ADRs in our study could not be definitely linked to specific causes due to the presence of confounding factors and the study's retrospective nature.

No statistically significant correlation was found between the number of pDDIs and the APACHE II score, SOFA scores on days 1, 7, 14, and the length of ICU stay. This may be attributed to the fact that we only included pDDIs caused by antibacterial and antifungal drugs, the relatively small number of patients, and the retrospective nature of our study.

Limitations

The strengths and weaknesses of our study are discussed in the following sentences. A strength of our study is that we searched for pDDIs according to the Lexicomp and Micromedex databases, which are recognized as reliable sources for detecting clinically significant DDIs, and interpreted them in the context of the intensive care patient profile. The most significant limitation of our study is its retrospective nature, which precluded the evaluation of the clinical manifestations of pDDIs. Another limitation is that the study is single-centered, potentially affecting the generalizability of the data.

Ideas for Further Research

Future studies should be designed to clearly distinguish whether a pDDI is clinically significant. In cases where this is not possible due to the multitude of confounding factors, investigating the relationship between pDDIs and clinical outcomes may be rational.

CONCLUSION

As a result of polypharmacy, which is an inevitable problem in critically ill patients, pDDIs between antibacterial and antifungal drugs and other drugs used were detected in 88% of patients according to at least one database. 62.4% of all detected pDDIs are classified as major according to at least one database, posing a potential risk for patient management. However, only 27.3% of the pDDIs were found at similar interaction levels in both databases. Accordingly, interactions should be checked not only against one database but also across multiple databases, guided by the opinion and experience of experienced clinical pharmacists. A good consultation system with the physicians, clinical pharmacists and nurses is crucial for enhancing the quality of pharmaceutical care in the hospital.

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Author Contributions: Concept – ŞB; Design – ŞB; Supervision – ŞB; Resource – KG, AUK; Materials – ŞB, ED; Data Collection and/or Processing – ŞB, ED; Analysis and/or Interpretation – ŞB, ED; Literature Search – ŞB, ED; Writing – ŞB, ED; Critical Reviews – ŞB, ED.

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