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Potential drug interactions related to antimicrobials use in hospitalized patients on hemodialysis

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Abstract

Objective: to evaluate the prevalence, severity and main clinical consequences of potential drug interactions (DIs) related to antimicrobials in hemodialysis patients admitted to a university hospital. **Methods:** This is an observational and retrospective study, conducted in a university hospital in the Midwest region, the sample consisted of adult patients using antimicrobial therapy and undergoing renal replacement therapy. DIs were verified in medical prescriptions, during a period of 7 days, using the Micromedex® database. **Results:** 85 patients were included in the study and 595 prescriptions were analyzed. As for kidney disease, 30 (35.3%) of the patients underwent hemodialysis for acute kidney injury, 45 (53%) for chronic kidney disease and in 10 (11.7%) it was not possible to verify the type of kidney disease due to lack of information in the charts. At least one DI were identified in 29.6% of prescriptions. In all, 499 interactions were found, of which 301 (60.3%) were important, 149 (29.9%) were moderate and 49 (9.8%) were contraindications. Regarding possible adverse events related to contraindicated interactions, 25 (51.0%) were related to an increase in hypertensive events and 8 (16.3%) to cardiotoxicity. The antimicrobials most involved in possible DI were fluconazole (98.76% of antifungals), ciprofloxacin (79.4% of quinolones) and linezolid (oxazolidones). The most frequent interactions were: linezolid and norepinephrine (contraindicated), ciprofloxacin and insulin (important), fluconazole and fentanyl (important), fluconazole and omeprazole (moderate). **Conclusion:** Most of the potential DIs identified were serious and there was a high percentage of contraindicated DIs. The main potential adverse events were related to the cardiovascular system. These findings reinforce the importance of knowing the possible antimicrobial-related DIs in hemodialysis patients, their possible adverse events and corresponding management.

Key words: Renal insufficiency; Renal dialysis; Patient safety; Drug-related side effects and adverse reactions.

Potenciais interações medicamentosas relacionadas ao uso de antimicrobianos em pacientes hospitalizados em hemodiálise

Resumo

Objetivo: avaliar a prevalência, gravidade e principais consequências clínicas das potenciais interações medicamentosas (IMs) relacionadas a antimicrobianos em pacientes em hemodiálise internados em um hospital universitário. **Métodos:** Trata-se de um estudo observacional e retrospectivo, conduzido em um hospital universitário da região Centro-Oeste, a amostra foi constituída de pacientes adultos em uso de terapia antimicrobiana e submetidos a terapia renal substitutiva. Foram verificadas as IMs em prescrições médicas, durante um período de 7 dias, utilizando a base de dados Micromedex®. **Resultados:** Foram incluídos 85 pacientes no estudo e analisadas 595 prescrições. Quanto à doença renal, 30 (35,3%) dos pacientes foram submetidos a hemodiálise devido lesão renal aguda, 45 (53%) devido a doença renal crônica e em 10 (11,7%) não foi possível verificar o tipo de doença renal em virtude da falta de informações em prontuários. Identificou-se ao menos uma IM em 29,6% das prescrições. Ao todo foram encontradas 499 interações, 301 (60,3%) importantes, 149 (29,9%) moderadas e 49 (9,8%) contraindicações. Em relação aos possíveis eventos adversos relacionados às interações contraindicadas 25 (51,0%) foram relacionadas ao aumento de evento hipertensivo e 8 (16,3%) à cardiotoxicidade. Os antimicrobianos mais envolvidos nas possíveis IMs foram fluconazol (98,76% dos antifúngicos), ciprofloxacino (79,4% das quinolonas) e linezolida (oxazolidonas). As interações mais frequentes foram: linezolida e norepinefrina (contraindicada), ciprofloxacino e insulina (importante), fluconazol e fentanil (importante), fluconazol e omeprazol (moderada). **Conclusão:** A maioria das potenciais IMs identificadas foram graves e houve alto percentual de IMs contraindicadas. Os principais potenciais eventos adversos foram relacionados ao sistema cardiovascular. Esses achados reforçam a importância do conhecimento das possíveis IMs relacionadas a antimicrobianos em pacientes em hemodiálise, seus possíveis eventos adversos e manejo correspondente.

Palavras chave: Insuficiência renal; Diálise renal; Segurança do paciente; Efeitos colaterais e reações adversas relacionados a medicamentos.

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Introduction

Patients with chronic kidney disease (CKD), are more likely to manifest drug-related problems (DRPs), and drug interactions (DIs) are among the most frequently identified DRPs in this profile of patients[1].

DIs occur when the effect of a drug is pharmacokinetically or pharmacodynamically modified by another drug[2]. ADRs are considered a harmful and non-intentional response to a medication, taking place at usual doses[3]. DIs can trigger the onset of type "F" ADRs due to an unexpected therapy failure, induced by the modification in the effect of the drug[4].

In the CKD stage, the comorbidities associated and polypharmacy are directly related to the risk of DIs and, consequently, to the manifestation of ADRs[1,5]. DIs and ADRs are important public health problems that threaten patient safety in the hospital environment and are responsible for significant morbidity and mortality worldwide, in addition to burdening health systems[6,7].

The conditions that affect the structure and function of the kidneys can be acute or chronic. Acute kidney injury (AKI) is characterized by a sudden reduction in the renal function, whereas in chronic kidney disease (CKD) these alterations exist for more than three months[8,9]. Aged patients who develop AKI frequently undergo more hospitalizations and are more likely to develop more severe CKD stages and associated comorbidities that lead to the use of countless medications[10].

Patients with a reduced glomerular filtration rate (GFR) present more risks of developing infections, and the infection incidence rate increases with severity of CKD. Among the most relevant infections in CKD we can mention those of the lower respiratory tract and of the urinary tract and sepsis[11].

In many cases, use of antibiotics is required due to infections in this profile of patients. As most of these medications are eliminated by the kidneys and some of them are nephrotoxic, they can be associated with severe ADRs in these patients[12]. A study that evaluated the prevalence of potential DIs involving antimicrobials and other standardized medications in a hospital identified that 19.7% of the antimicrobials in the unit were involved in potential clinically relevant DIs[13].

In the world, it is estimated that CKD affects more than 10% of the population[14] and, in Brazil, the last national chronic dialysis survey revealed that the estimated incidence and prevalence rates of patients on dialysis continue to grow[15] and with that, consequently, also the use of antimicrobials, which favors the emergence of potential DIs involving this class of medications. Thus, the objectives of this study were as follows: to describe the prevalence, severity and main clinical consequences of potential DIs related to antimicrobials, found in the Micromedex® database, and the demographic and clinical profile of patients on hemodialysis (HD) admitted to a university hospital from the Midwest region.

Methods

An observational and retrospective study conducted in a university hospital from the Midwest region. The sample consisted of patients hospitalized in the following units: medical clinic, surgical clinic I, adult emergency room, infectious parasitic diseases, adult intensive care unit and coronary care unit, using antimicrobial therapy and undergoing renal replacement therapy from January to August 2017.

For data collection, the HD sector was verified in relation to inpatients undergoing HD from January to August 2017. From this list, patients under 18 years of age were excluded, as well as those for whom antimicrobials were not prescribed and those who did not have all the information necessary for the study in their medical records.

Data collection was performed manually by filling in a form previously prepared by the researchers. Data from all the inpatients during the aforementioned period and that met the inclusion criteria were collected. Study variables referring to a period of 7 consecutive days were collected. The first day considered was the date when hemodialysis was performed and at least one antimicrobial was administered. For the patients hospitalized for more than 30 days, data from 7 days were collected for each 30-day period.

The variables collected were the following: sociodemographic and clinical characteristics, which in turn included a) gender (male and female) b) age (measured in years old), and c) (underlying disease and comorbidities) and pharmacological variables related to all the medications prescribed. The sociodemographic and clinical variables were collected at a single moment, whereas the pharmacological ones were collected via the analysis of the daily prescriptions at 7 days of monitoring.

Subsequently, the data were separated into two groups: sociodemographic/clinical and pharmacological characteristics; and, for better organization, they were typed into different Microsoft Excel® 2013 spreadsheets. Seven spreadsheets were prepared for the pharmacological characteristics, each one referring to one monitoring day. The potential DIs were verified by the pharmacists resorting to the Micromedex® database[16]. This database classifies potential DIs according to severity level into four groups: A) Contraindicated - Concomitant use of the medications is contraindicated; B) Important - It poses a risk to life and/or requires intervention to minimize or prevent serious adverse events; C) Moderate - It can cause exacerbation of the patient's condition and/or requires changes in the treatment; and D) Secondary - The interaction has limited clinical effects and, in general, no changes in the treatment are necessary[16].

An individual analysis was performed in which all the medications prescribed daily for each patient were crossed between each other. In this stage, all the potential DIs registered in the database were obtained, only selecting those that involved antimicrobials.

The moderate, important and contraindicated DIs were collected. The secondary ones were excluded from the research. For each interaction, the main clinical consequences were collected, in addition to describing the clinical management options proposed by the database. They were stored in a Microsoft Excel® 2013 spreadsheet for their subsequent statistical analysis.

The data were analyzed in the SPSS (*Statistical Package for the Social Sciences* 20.0) software, version 20.0 from 2011, and submitted to simple descriptive analysis.

For the qualitative variables, absolute and relative frequency tables were obtained and, for the quantitative variables, central tendency and dispersion measures were calculated. The Shapiro-Wilk test was used was used to analyze normality of the variables.

To compare the changes in the variables between the first day and the seventh day of the study, the paired Student's t-test or Wilcoxon test was used for quantitative variables, according to normality, and the McNemar test for qualitative variables. p-values < 0.05 were considered as statistically significant differences.

This study was approved by the Research Ethics Committee of the Federal University of Mato Grosso do Sul, according to opinion No. 2,355,479, and by the Teaching and Research Management Office of the Maria Aparecida Pedrossian University Hospital.

Results

From January to August 2017, 120 patients underwent HD; among these, 99 (82.5%) used some antimicrobial, of which 14 were excluded due to lack of data. Consequently, 85 patients that met the inclusion criteria were included to analyze the DIs. Of these, 51 (60.0%) were aged ≥ 60 years old and 34 (40.0%) were between 18 and 59 years old, with a mean of 61.2 ± 15.2. There was predominance of the male gender (n=53; 62.4%). Regarding diseases, 56 (65.9%) of the patients were hypertensive or diabetic and 37 (66.1%) of them had both diseases. In terms of kidney disease, 30 (35.3%) underwent HD due to AKI, 45 (53%) due to CKD, and it was not possible to identify the reason in 10 (11.7%) patients due to lack of information in medical records.

A total of 595 prescriptions had been analyzed at the end of the study. At least one potential DI related to antimicrobials was identified in 176 (29.6%) of the prescriptions and in 38 (44.7%) of the patients during all 7 days. A total of 499 potential DIs related to antimicrobials were found, with 301 (60.3%) important, 149 (29.9%) moderate and 49 (9.8%) contraindicated. The frequency and severity of the potential DIs identified throughout all 7 seven days are described in Table 1. The mean number of potential DIs per day was 71.3 ± 5.8. On the first monitoring day, 28.2% of the patients presented at least one DI; in turn, this value was 32.9% in the last day, with a consequent 4.7% increase, p=0.523.

Table 1. Frequency of the possible drug interactions according to severity in the 7-day period.

Day	Severity of the interaction			Total DIs
	Contraindicated DIs	Important DIs	Moderate DIs	
1	6 (8.6%)	44 (62.8%)	20 (28.6%)	70 (14.0%)
2	3 (4.2%)	48 (66.6%)	21 (29.2%)	72 (14.4%)
3	8 (11.9%)	41 (61.2%)	18 (26.9%)	67 (13.4%)
4	7 (9.1%)	47 (61.0%)	23 (29.9%)	77 (15.4%)
5	7 (10.9%)	36 (56.2%)	21 (32.8%)	64 (12.8%)
6	7 (10.4%)	39 (58.2%)	21 (31.3%)	67 (13.4%)
7	11 (13.4%)	46 (56.1%)	25 (30.5%)	82 (16.4%)
Total	49 (9.8%)	301 (60.3%)	149 (29.9%)	499 (100%)

In relation to the adverse events, 39 (26.2%) of the potential moderate DIs were related to the increase in omeprazole availability, followed by hypoglycemia risk in 25 (16.8%). In the potential important DIs, the highest prevalence corresponded to QT interval prolongation and arrhythmias 101 (33.6%), followed by hypoglycemia or hyperglycemia in 37 (12.3%), as detailed in Table 2.

Table 3 describes the possible adverse events related to the contraindications identified in this study; 25 (51.0%) of these potential DIs were related to increased hypertensive events and 8 (16.3%) to cardiotoxicity. In 10 (20.4%) of these DIs, the database used indicated absolute contraindication in the association of these drugs: linezolid and methyldopa, linezolid and tramadol, fluconazole and domperidone, and fluconazole and haloperidol. It is noted that the potential DI between linezolid and methyldopa (absolute contraindication) was identified on the fifth monitoring day for a specific patient.

Regarding the drug-related profile, it was verified that the mean number of antimicrobials prescribed per patient decreased over the course of the 7 days, from 2.5 ± 1.5 on the first day (minimum = 1, maximum = 8), to a mean of 1.9 ± 1.9 on the last day analyzed (minimum = 1, maximum = 7), representing a reduction in the mean of 0.7±1.5, p=0.000. The main indication for using antimicrobials in the evaluated patients was sepsis, corresponding to 29 (34.1%).

Table 2. Frequency of the possible adverse events of the important DIs in the 7-day period.

Adverse event	Day							
	1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)	6 n (%)	7 n (%)	Total n (%)
QT prolongation and arrhythmias	16 (15.8%)	15 (14.8%)	13 (12.9%)	17 (16.8%)	11 (10.9%)	14 (13.9%)	15 (14.8%)	101 (33.6%)
Glycemia changes	6 (16.2%)	6 (16.2%)	4 (10.8%)	5 (13.5%)	4 (10.8%)	6 (16.2%)	6 (16.2%)	37 (12.3%)
Myopathy and rhabdomyolysis	3 (9.1%)	6 (18.2%)	5 (15.1%)	6 (18.2%)	4 (12.1%)	4 (12.1%)	5 (15.1%)	33 (10.9%)
Fentanyl-induced toxicity	7 (23.3%)	6 (20.0%)	5 (16.7%)	3 (10.0%)	3 (10.0%)	3 (10.0%)	3 (10.0%)	30 (10%)
Variation in the non-antimicrobial drug concentration	2 (9.5%)	4 (19.0%)	4 (19.0%)	3 (14.3%)	3 (14.3%)	3 (14.3%)	2 (9.5%)	21 (6.9%)
Serotonin syndrome	1 (5.0%)	3 (15.0%)	2 (10.0%)	3 (15.0%)	4 (20.0%)	3 (15.0%)	4 (20.0%)	20 (6.6%)
Tramadol-induced toxicity	3 (18.8%)	3 (18.8%)	1 (6.2%)	2 (12.5%)	2 (12.5%)	2 (12.5%)	3 (18.8%)	16 (5.3%)
Oto- and nephrotoxicity	1 (7.1%)	2 (14.3%)	4 (28.6%)	2 (14.3%)	1 (7.1%)	1 (7.1%)	3 (21.4%)	14 (4.7%)
Nephrotoxicity	0 (0%)	1 (11.1%)	2 (22.2%)	2 (22.2%)	2 (22.2%)	1 (11.1%)	1 (11.1%)	9 (3.0%)
Reduction in fentanyl concentration	3 (37.5%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	0 (0%)	8 (2.7%)
Morphine-induced toxicity	1 (20.0%)	1 (20.0%)	-	1 (20.0%)	-	-	2 (40.0%)	5 (1.7%)
Reduction in tramadol concentration	-	-	-	1 (33.3%)	1 (33.3%)	-	1 (33.3%)	3 (0.9%)
Reduced efavirenz concentration	-	-	-	1 (50.0%)	-	1 (50%)	-	2 (0.6%)
Hypertensive crisis	1 (100%)	-	-	-	-	-	-	1 (0.3%)
Megaloblastic anemia and pancytopenia	-	-	-	-	-	-	1 (100%)	1 (0.3%)
Total	44 (14.6%)	48 (15.9%)	41 (13.6%)	47 (15.6%)	36 (12.0%)	39 (13.0%)	46 (15.3%)	301 (100%)

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Table 3. Frequency of the possible adverse events of the contraindicated DIs in the 7-day period.

Adverse event	Day							
	1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)	6 n (%)	7 n (%)	Total n (%)
Increase in hypertensive effects	2 (8%)	1 (4.0%)	3 (12.0%)	4 (16.0%)	5 (20.0%)	4 (16.0%)	6 (24.0%)	25 (51.0%)
Cardiotoxicity	-	-	3 (37.5%)	2 (25%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	8 (16.3%)
Hypertensive crisis	1 (16.7%)	1 (16.7%)	2 (33.3%)	1 (16.7%)	-	-	1 (16.7%)	6 (12.2%)
QT interval prolongation	2 (66.7%)	1 (33.3%)	-	-	-	-	-	3 (6.1%)
Serotonin syndrome	-	-	-	-	1 (33.3%)	1 (33.3%)	1 (33.3%)	3 (6.1%)
Serotonin syndrome or opioid-induced toxicity	-	-	-	-	-	1 (50.0%)	1 (50.0%)	2 (4.1%)
Excessive sedation	1 (100%)	-	-	-	-	-	-	1 (2.0%)
Increase in exposure to haloperidol and QT prolongation	-	-	-	-	-	-	1 (100%)	1 (2.0%)
Total	6 (12.2%)	3 (6.1%)	8 (16.3%)	7 (14.3%)	7 (14.3%)	7 (14.3%)	11 (22.4%)	49 (100%)

The most prescribed antimicrobial classes on the first day were carbapenems with 29 (13.2%) and penicillins with 23 (10.5%) and, on the seventh day, carbapenems with 27 (17.3%) and lipopeptides with 17 (10.9%). The most prevalent classes of antimicrobials in the DIs over the 7 days were as follows: antifungal with 162 (28.6%), followed by fluoroquinolones with 97 (17.1%) and oxazolidinone with 76 (13.4%) (Table 4). The medications from these classes that were most involved in the DIs were fluconazole (98.76% of antifungals), ciprofloxacin (79.4% of quinolones) and linezolid (oxazolidinones).

The most frequent potential DIs during the 7-day follow-up period were the following: linezolid and norepinephrine (contraindicated), ciprofloxacin and insulin (important), fluconazole and fentanyl (important), and fluconazole and omeprazole (moderate), as described in Figure 1.

Table 4. Profile of the antimicrobials prescribed on the first and seventh day related to the total of drug interactions in the 7-day period.

Classe	ATM		IM
	Dia 1 - n (%)	Dia 7 - n (%)	Total - n (%)
Aminoglicosídeos	16(7,3%)	11(7,1%)	27 (4,8%)
Antifúngicos	20(9,1%)	13(8,3%)	162 (28,6%)
Antimicobacterianos	2(0,9%)	2(1,3%)	40 (7,1%)
Antiparasitários	2(0,9%)	2(1,3%)	-
Antirretrovirais	10(4,6%)	6(3,8%)	32 (5,6%)
Antivirais	7(3,2%)	4(2,6%)	-
Carbapenêmicos	29(13,2%)	27(17,3%)	-
Cefalosporinas	16(7,3%)	4(2,6%)	-
Daptomicina	3(1,4%)	3(1,9%)	5 (0,9%)
Fluoroquinolonas	9(4,1%)	6(3,8%)	97(17,1%)
Glicopeptídeo	21(9,6%)	16(10,3%)	16 (2,8%)
Lipopeptídeos	21(9,6%)	17(10,9%)	-
Lincosamidas	8(3,7%)	3(1,9%)	-
Macrolídeos	11(5,0%)	4(2,6%)	33 (5,8%)
Nitroimidazolico	4(1,8%)	5(3,2%)	45 (7,9%)
Oxazolidinonas	4(1,8%)	6(3,8%)	76 (13,4%)
Penicilinas	23(10,5%)	14(9,0%)	5 (0,9%)
Pirimetamina	2(0,9%)	2(1,3%)	1 (0,2%)
Sulfonamida	8(3,7%)	8(5,1%)	28 (4,9%)
Tigeciclina	3(1,4%)	3(1,9%)	-
Total	219(100%)	156(100%)	567 (100%)

Discussion

In this study, the sociodemographic profile observed was similar to the one found in a study conducted with outpatients with chronic kidney disease, where there was predominance of males (54.7%) and of aged individuals (69.4%), and the most prevalent comorbidities were hypertension (68.5%) and diabetes (31.9%)[17]. Similarly, a Nigerian study conducted with chronic renal patients treated in a tertiary-level hospital with approximately 70% subjects with stage 5 CKD (GFR < 5 mL/min) found a high prevalence of male patients (66.7%) and comorbidities such as hypertension (SAH) (83.7%) and diabetes (DM) (31.7%)[18]. These data can be justified because both diseases are the main causes of chronic kidney disease and the male lifestyle is more prone to smoking, alcohol use, and evasion from health services[18].

It was identified that almost one third of the prescriptions contained at least one potential DI related to antimicrobials. In a study conducted in a Nephrology unit of a tertiary-level hospital that aimed at evaluating DIs in patients with CKD, 60% of them were hospitalized for more than 5 days, 78.5% prevalence of DI was identified, 541 and possible DIs were detected: 56.6% moderate, 24.0% secondary, 13.9% important and 5.5% contraindicated[19]. The prevalence of potential DIs found in our study was lower mainly because we only evaluated interactions involving antimicrobials and because of the fact that, due to clinical relevance, secondary interactions were excluded.

The profile of the interactions found in this study was predominantly of potential important DIs, unlike others where the most frequent DIs were moderate[19,20].

A study that evaluated the medications used and the possible DIs in patients on hemodialysis at the outpatient level identified prevalence of DIs in 56.9% of the patients, totaling 112 DIs: 49.1% moderate, 27.6% important and 1.7% contraindicated[21]. The high prevalence of potential important and contraindicated DIs identified in our study can be justified by the profile of the medications prescribed, as the patients were hospitalized and most of them were using multiple drugs, including broad-spectrum antibiotics due to sepsis.

In relation to the adverse events of the important potentials DIs prevalent in this study, it was found that the highest prevalence was QT interval prolongation, due to the interaction between metronidazole and ondansetron. A study that aimed at evaluating DIs and QT interval prolongation in an Intensive Care Unit (ICU) identified that one of the main pharmacokinetic DIs responsible

Figure 1. Most frequent interactions throughout all 7 days, severity, adverse event and management.

Medication pairs	Severity[1]	Adverse event[1]	Management[1]
Ciprofloxacin and Insulin	Important	Glycaemia changes	Monitor glucose level. Adjust insulin dose as indicated. In case of hypoglycemia, initiate the appropriate therapy and suspend fluoroquinolone.
Fluconazole and Fentanyl	Important	Fentanyl-induced toxicity	Monitor adverse effects (sedation and respiratory depression).
Fluconazole and Omeprazole	Moderate	Increased omeprazole concentration	Consider the possibility of using omeprazole in case of Zollinger-Ellison syndrome. Monitor increased adverse effects of omeprazole (elevated liver enzymes, headache, diarrhea, abdominal pain)
Fluconazole and Midazolam	Moderate	Excessive sedation and prolonged hypnotic effects	Consider the possibility of reducing midazolam dose and monitoring increased midazolam toxicity (excessive sedation and prolonged hypnotic effects)
Metronidazole and Ondansetron	Important	QT interval prolongation (Torsades de pointes)	Susceptible patients may need electrocardiographic monitoring
Sulfamethoxazole + Trimethoprim and Insulin	Moderate	Hypoglycemia	Monitor glucose levels and adjust insulin dose
Linezolid and Fentanyl	Important	Opioid effects and serotonin syndrome	If possible, replace serotonergic opioid (fentanyl) with non-serotonergic (morphine). Monitor serotonin syndrome symptoms. If it is developed, provide supportive care.
Linezolid and Norepinephrine	Contraindicated	Increase in hypertensive effects	The initial norepinephrine doses should be reduced and subsequently titrated to achieve the desired response.
Linezolid and Insulin	Moderate	Hypoglycemia	Monitor glucose level. Lower insulin doses may be necessary.
[1]Micromedex®			

for this adverse event (AE) was also the association between metronidazole and ondansetron (18.2%); however, this same study concluded that the main DIs associated with QT interval prolongation are of pharmacodynamic origin, involving blockage of the potassium channels, through drugs such as: ondansetron, metoclopramide, ciprofloxacin and amiodarone[22]. This study also included patients who did not have kidney disease and did not specify whether there were patients on HD, so that possible AEs could be potentiated in this profile of patients, as the serum concentrations of drugs or metabolites contributing to this AE could be increased due to reduced excretion [23]. Adequate dose adjustment and electrocardiographic monitoring could be used as a strategy to prevent QT interval prolongation and arrhythmias in susceptible patients [23].

Regarding the potential AEs caused by the contraindicated combinations, an increase in the hypertensive effect (linezolid and noradrenaline), cardiotoxicity and hypertensive crisis (linezolid and methyldopa) stood out. It is noted that the management proposed for the increase in the hypertensive effect is titration of norepinephrine according to the patient's pressure levels[16]; as for the adverse effect of hypertensive crisis caused by the interaction (linezolid and methyldopa), the database used in this research proposed absolute contraindication, that is, there is no management for this interaction[16].

Other potential AEs prevalent in our study were glycemic changes and myopathy/rhabdomyolysis. A study that evaluated the incidence of DIs involving several medications in young and aged patients treated in the emergency department of a tertiary-level hospital in the Caribbean found results that were partially similar to ours, identifying high incidence of severe DIs that progressed with bleeding (41.9%), and rhabdomyolysis (22.4%)[24]. Likewise, another study that evaluated potential DIs involving all the medications prescribed on the third hospitalization day of patients in an ICU, using 3 different databases, concluded that the possible AEs of the most frequent important and contraindicated DIs were as follows: cardiotoxicity and QT interval prolongation, respiratory depression, hemorrhage and also myopathy/rhabdomyolysis[25], data that are similar to the findings of our study, although we have only included DIs involving antimicrobials.

Regarding the profile of the antimicrobials prescribed, the highest prevalence on the first and seventh days corresponded to carbapenems; however, potential DIs were not observed in this class. The main classes related to potential DIs were antifungals, fluoroquinolones and oxazolidones. It was also observed that, despite the reduction in the number of antimicrobials prescribed on the last day when compared to the first, there was an increase in the prescription of antimicrobial classes more related to DIs, which can justify the increase in DIs on the last day in relation to the first. A study carried out with patients admitted to an ICU of a tertiary-level hospital found similar results to our study: DIs involving fluconazole, linezolid associated with contraindicated DIs and metronidazole with severe DIs. As well as ours, this study showed high prevalence of AEs associated to the cardiovascular system[26].

According to a study carried out in an ICU of a university hospital, antibiotics were the second most prescribed class in the unit (10.61%), only second to electrolyte replacement (25.19%)[27]. This reinforces the need for knowledge, identification and monitoring of the potential DIs related to this class, in order to avoid future AEs that could jeopardize the treatment or safety of patients in hospital institutions.

In this study carried out in an ICU, the interactions involving fluconazole and fentanyl and fluconazole and omeprazole were among the most relevant[27], as identified in our study. Fluconazole inhibits the enzyme complex of cytochrome P450-3A4 (CYP4503A4), responsible for the biotransformation of fentanyl; thus, there is an increase in the serum levels of this drug, which poses a higher risk of AEs and hypersedation. It is noted that the possibility of the manifestation of this DI is greater after 120 hospitalization hours[28].

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Among the most frequent interactions identified in the current study, the association between ciprofloxacin and insulin stands out. Likewise, a study conducted with hypertensive patients admitted to a hospital in India found similar results: the medication that was most associated with DIs was insulin (33.96%), and the most detected interaction was also ciprofloxacin and insulin[29].

Similarly, a cohort study found an association between dysglycemia and use of fluoroquinolones in diabetic patients. It is noted that the patients suffering from chronic kidney disease and those treated concomitantly with hypoglycemic agents were more vulnerable to changes in glucose homeostasis[30]. The aforementioned data reinforce the need to monitor plasma glucose levels in HD patients when using antimicrobials from the fluoroquinolone class, as most of these patients have chronic diseases such as hypertension and diabetes and clinical conditions that favor the interactions[31].

Most of the patients in this study were male, hypertensive or diabetic, and had CKD. In relation to the potential DIs identified, most of them were classified as important by the database. The main AEs related to the potential moderate DIs were increased omeprazole bioavailability at risk of hypoglycemia; in the potential important DIs, the highest prevalence values were in QT interval prolongation and arrhythmias and also hypo- or hyperglycemia; whereas hypertensive events stood out among the contraindications. The most prescribed class of antimicrobials corresponded to carbapenems, although the class most involved in potential DIs was antifungal drugs.

The number of potential antimicrobial-related DIs in HD patients is associated with their comorbidities, prescribed medications and, especially, with the class of antimicrobial in use, as the class of antimicrobial most prescribed in this study was not related to DIs. This fact suggests that, when prescribed, some antimicrobials should be primarily monitored for possible interactions.

Despite the limitations of this study, as some information was not included in the patients' medical records, the DIs identified were theoretical and the manifestation of the reactions was not evaluated, the results obtained are relevant in the clinical practice, as a high percentage of potential important and contraindicated DIs was identified, whose adverse events may endanger patient safety, prolong the stay in the hospital unit and increase health care costs; in addition , many of the studies found focus on patients with CKD, most of them outpatients. There were no studies on antimicrobial-related DIs that included hospitalized HD patients, either CKD patients or HD AKI.

Conclusion

This study identified that approximately 50% of the hospitalized patients using antimicrobials and undergoing hemodialysis are prone to DIs. Most of the DIs identified would be potentially severe if they occurred, and there was a high percentage of contraindicated DIs. The main consequences of these potential interactions were adverse events related to the cardiovascular system and changes in plasma glucose. These findings reinforce the importance of knowing the potential DIs related to antimicrobials in patients undergoing HD, their possible adverse events and their proper management.

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Collaborators

PRM, EAMD, LTF and CCMS conceived the project; CCMS and PRM collected the data; PRM, EAMD, LTF and CCMS analyzed and interpreted the data; PRM and EAMD wrote the article; and PRM, CCMS, EAMD and LTF critically reviewed the article and approved its final version. The authors are responsible for all the aspects of the paper in ensuring the accuracy and integrity of any of its parts.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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