Original Paper

# Antimicrobial related problems in patients undergoing renal dialysis in a university hospital

Cristiane CABRERA DOS SANTOS[1]
Elza APARECIDA DOMINGUES[2]

1 Universidade Federal de Mato Grosso do Sul
2 Hospital Universitário Maria Aparecida Pedrossian - Universidade Federal de Mato Grosso do Sul

## Abstract

**Objective**: To detect antimicrobial drug-related problems (DRP) in adult patients undergoing renal dialysis in a university hospital. **Methods**: This is an observational and retrospective study in which were included patients hospitalized in antimicrobial therapy and submitted to renal replacement therapy (RRT) from January to August 2017. The study variables were collected on the first day that antimicrobial was administraded and hemodialysis was done. The Dáder Methodology was used to detect and classify the DRP and probable negative outcomes associated with medications (NOMs). **Results**: 85 patients were included, 62.4% (n=53) male, mean age 61.2 ± 15.2 years. An average of 2.6 ± 1.6 different antimicrobials prescribed per patient was observed, being the main class carbapenems (13.7%) and the main reason for antimicrobial use was sepsis (34.1%). The main DRPs found were: prescription error (45.1%), Y incompatibility (14.0%) and inadequate dosage (12.1%), median 6.0 (4-11) DRP per patient, minimum:1 and maximum:32. Regarding NOMs, the most frequent were quantitative insecurity (50.6%), non-quantitative insecurity (19.9%) and quantitative ineffectiveness (19.0%). **Conclusions**: All patients undergoing dialysis and antimicrobial therapy included in this study had at least one problem related to antimicrobial drugs and, therefore, one probable NOM. It was verified the need of a multiprofessional team working on the detection and prevention of avoidable problems, through the implantation of computerized systems, continuing education program, protocols and routines, allied with an institutional antimicrobial stewardship program.

**Key words**: renal replacement therapy, anti-infective agents, renal dialysis, medication errors.

## Problemas relacionados ao uso de antimicrobianos em pacientes submetidos à dialise renal em um hospital universitário

## Resumo

**objetivos**: Detectar os problemas relacionados a medicamentos (PRM) antimicrobianos em pacientes adultos submetidos à diálise em um hospital universitário. **Metodologia**: Estudo observacional, retrospectivo, no qual foram incluídos pacientes internados, em terapia antimicrobiana e submetidos à terapia renal substitutiva (TRS), no período de janeiro a agosto de 2017. As variáveis do estudo foram coletadas no primeiro dia em que foi administrado o antimicrobiano e realizado a hemodiálise. Para a detecção e classificação dos PRM e prováveis resultados negativos associados a medicamentos (RNMs) utilizou-se a Metodologia Dáder. **Resultados**: Foram incluídos 85 pacientes, 62,4% (n=53) do sexo masculino, idade média de 61,2 ± 15,2 anos. Observou-se uma média de 2,6 ± 1,6 antimicrobianos diferentes prescritos por paciente, sendo a principal classe os carbapenêmicos (13,7%) e o principal motivo do uso de antimicrobiano foi sepse (34,1%). Os principais problemas relacionados a medicamentos antimicrobianos encontrados foram: erro na prescrição (45,1%), incompatibilidade em Y (14,0%) e posologia não adequada (12,1%), mediana de 6,0 (4-11) PRM por paciente, mínimo:1 e máximo:32. Quanto aos RNMs, os mais frequentes foram: insegurança quantitativa (50,6%), insegurança não quantitativa (19,9%) e inefetividade quantitativa (19,0%). **Conclusões**: Todos os pacientes submetidos à diálise e terapia antimicrobiana incluídos no estudo apresentaram pelo menos 1 (um) problema relacionado a medicamentos antimicrobianos e, consequentemente 1 (um) provável RNM. Verificou-se a necessidade da equipe multiprofissional atuando na detecção e prevenção de problemas evitáveis, mediante a implantação de sistemas informatizados, programa de educação continuada, protocolos e rotinas, aliados ao um programa de gerenciamento de antimicrobianos institucional.

**Palavras-chave**: terapia de substituição renal, anti-infecciosos, diálise renal, erros de medicação.

Submitted: 11/09/18
Resubmitted: 19/11/19
Accepted: 31/12/19
Blind reviewers

DOI: 10.30968/rbfhss.2019.104.0340
ISSN online: 2316-7750

Corresponding Author:
Cristiane Cabrera de Mello dos Santos
crismello89@hotmail.com

## Introduction

In the Brazilian Chronic Dialysis Survey 2017, Thomé et al. (2019) observed the trend of continuous increase in the number of patients on dialysis. A total of 126,583 patients on chronic dialysis were estimated in 2017, an increase of 159.4% over 2002. In the centers participating in the survey, 93.1% of the patients were on hemodialysis[1].

The progressive and irreversible loss of kidney function characterizes Chronic Kidney Disease (CKD), assessed using the Glomerular Filtration Rate (GFR), requiring highly complex therapies. Depending on the stage of the disease, renal replacement therapy is indicated[2].

In patients undergoing Renal Replacement Therapy (RRT) it is extremely important to know the type of RRT (hemodialysis, dialysis or ultra-filtration) and the interaction between the filter and the membrane (molecular weight, blood flow and dialysate flow), since these aspects collaborate for the assessment of the need to adjust the dose or the medication administration schedule during this procedure[3].

Carvalho et al. highlighted the importance of identifying medication - medication or medication - hemodialysis process interactions, whether the drug is dialysable or not, recognizing the clinical relevance of the interaction, changes in absorption, distribution, metabolism, elimination, half-life and signs and symptoms resulting from these interactions[3].

For the choice of the antimicrobials (ATMs) dosage, characteristics such as weight, renal function, hypoalbuminemia, and finally, the potential for toxicity, should be considered. When there is kidney disease, the tendency is for the patients to have a greater potential for Adverse Drug Reactions (ADRs), especially when a combined therapy with antimicrobials is adopted[4].

According to the 3rd Granada Consensus, a Drug-Related Problem (DPR) is defined as all situations that cause or may cause the appearance of a Negative Outcome associated with the Medication (NOM), such as wrong administration of medication or prescription error. NOMs are health problems, unwanted changes in the patient's health status, attributable to the use (or disuse) of medications[5].

DRPs may or may not be preventable and may or may not harm patients' health. The Adverse Drug Reactions (ADRs) are considered non-preventable DRPs. Medication Errors (MEs) are considered preventable and may or may not cause harm to patients. Wrong dilution, wrong infusion time, concomitant administration of incompatible drugs in Y connection, among others, are classified as MEs, as they may occur due to prescription and/or administration errors[6].

Despite the risk of patients undergoing RRT when using antimicrobials to have a DRP, we have not found studies that detailed these problems and their possible consequences in hospitalized patients. Thus, the main objective of this work was to describe the problems related to the use of antimicrobials in adult patients undergoing renal dialysis in a university hospital.

## Methods

This is an observational and retrospective study that was carried out in a university hospital in the Midwest region. The sample consisted of hospitalized patients using antimicrobial therapy and undergoing renal replacement therapy from January to August 2017.

For data collection, the list of patients who were hospitalized during the study period and who underwent RRT was checked in the unit responsible for hemodialysis (HD). From this relationship, patients under 18 years old, those who did not have a prescription for antimicrobial therapy and those who did not have all the necessary data to carry out the study were excluded. The data available in electronic medical records, physical records and the hospital's internal system were used as an information source.

For data collection, a specific form was prepared. The study variables were collected on the first day that one or more antimicrobials were performed and also hemodialysis. For patients hospitalized during more than 30 days, data from the first day were collected for each period of 30 days.

The variables collected were the following: sociodemographic (gender and age), clinical (diagnosis of kidney disease, body mass index (BMI) and comorbidities), laboratory (serum levels of creatinine, urea, C-reactive protein (CRP), pro-calcitonin (PCAL), sodium, potassium, magnesium and blood count), pharmacological (ATMs prescribed, other prescription drugs: to assess drug interactions and Y-connection incompatibilities, dosage, dilution, infusion time, schedule), related to RRT (dialysis date and volume dialysed), pertinent to the related problems related to detected drugs (type of DRP, related drug(s) and possible NOM).

For the detection of problems related to antimicrobial drugs and probable NOMs, the Dáder Methodology[5] was used assessing the need, effectiveness and safety of the use of antimicrobials. The problems related to antimicrobial drugs were classified as: wrong medication administration (schedule), inadequate dose, inadequate dosage, duplicity (when the ATM was prescribed and the administration was checked twice), prescription error (wrong dilution, wrong infusion time, missing information and not having a supplementary dose), drug interaction and incompatibility with Y connection. The Noms were classified as: untreated health problem, medication without indication for the health problem, non-quantitative ineffectiveness, quantitative ineffectiveness, non-quantitative insecurity and quantitative insecurity. As a source of information for the assessment of dose, dosage, dilution and infusion rate, the Sanford Guide for Antimicrobial Therapy 2017 was used[7].

The Safety Protocol for the Prescription, Use and Administration of Medications[8] was used for analysis of errors in the prescription such as lack of essential items for the safe prescription of drugs, like the use of abbreviations, dosage, dilution, speed or time of infusion, route of administration, among others.

The study variables were stored in a database created in the Microsoft Office Excel software. The statistical analysis was performed using the IBM SPSS Statistics 20 program. The data were submitted to simple descriptive analysis. For the qualitative variables, absolute and relative frequency tables were obtained and, for the quantitative variables, measures of central tendency and dispersion were calculated. The normality of the variables was assessed by the Shapiro-Wilks test. To analyze quantitative variables, the Student's T test or the Mann-Whitney test were used, according to normality. For the qualitative variables, the Pearson's Chi-square or the Fisher's tests were applied. Values of $p < 0.05$ were considered statistically significant.

The present study was approved by the Research Ethics Committee of the Federal University of Mato Grosso do Sul, under opinion number 2,355,479, and by the Teaching and Research Management of the referred hospital.

## Results

During the study period, 120 patients underwent RRT, of whom 99 (82.5%) used antimicrobial therapy during hospitalization. 14 patients were excluded due to the lack of the necessary data to carry out the research, making up a sample of 85 patients included in the research at the end.

The sample was predominantly of male patients (n=53; 62.4%) with a mean age of 61.2 ± 15.2 years old. The main indication for the use of antimicrobials in the evaluated patients was sepsis, corresponding to 29 (34.1%), the urinary focus being the main one. The empirical treatment of pneumonia not associated with mechanical ventilation was the second most prevalent indication for the use of antimicrobials (n=25; 29.4%). In only 14 patients (16.5%), the prescribed antimicrobial was guided by the result of microbiological culture.

The empirical use of the collected ATMs used by the patients included in the study is justified in most patients because, when we analyze the blood count and the CRP and PCAL values, the median of these variables is high, which indicates signs of infection. The need for RRT is also considered when analyzing the variables of urea, creatinine, sodium, potassium and magnesium (Table 1).

Regarding the medication profile, a mean of 2.6 ± 1.6 different antimicrobials prescribed for each patient (minimum = 1, maximum = 8) was observed. The most prescribed classes were carbapenems (n=30; 13.7%) and glyco/lipopeptides (n=24; 11.0%) and penicillins (n=23; 10.5%). The drugs most used in these classes were the following: meropenem (80.0% of the carbapenems), teicoplanin (62.5% glycopeptides) and piperacillin + tazobactam (87.0% of thepenicillins). A significant use of polymyxins (9,6%), antifungals (9,1%), others (8,7%) and cephalosporins (7,8%) was observed (Table 2).

Regarding the profile of problems related to antimicrobial drugs, a median of total drug-related problems of 6.0 (4 - 11) per patient (minimum 1, maximum 32) was observed, where the most prevalent were errors in prescription (45.1%), Y incompatibility (14,0%) and inadequate dosage (12.1%) (Table 2). All the pharmacological classes presented errors in the prescription as their main problem. The penicillins and other medications (among which was sulfamethoxazole + trimethoprim intravenous) were the classes most related to Y incompatibility. On the other hand, antifungals were mainly related to the drug interactions detected. The carbapenems were related to both inadequate dosage and inadequate dose (Table 2). Among the errors in the prescriptions observed were missing information (dilution and infusion time: 90.9%), wrong dilution (4.9%), missing supplementary dose (2.1%) and wrong infusion time (2.1%) (Table 3).

**Table 1.** Sociodemographic, clinical and laboratory characteristics of the patients included in the study, total and stratified values according to the number of DRPs and the number of prescription errors (n=85)

| Data | All n=85 | Patients with > 2 DRPs n=78 | Patients with ≤ 2 DRPs n=7 | p-value | Prescription error > 1 n=67 | Prescription error ≤ 1 n=18 | p-value |
|---|---|---|---|---|---|---|---|
| **Sociodemographic** | | | | | | | |
| Male gender, n (%) | 53 (62.4) | 49 (57.6) | 4 (4.7) | 1.0 | 41 (48.2) | 12 (12.1) | 0.67 |
| Female gender, n (%) | 32 (37.6) | 29 (34.1) | 3 (3.5) | | 26 (30.6) | 6 (7.1) | |
| Age, years old, mean value (SD) | 61.2 ± 15.2 | 61.6 ± 15.4 | 57.1 ± 13.8 | 0.424 | 61.7 ± 14.9 | 59.3 ± 16.8 | 0.587 |
| **Clinical** | | | | | | | |
| BMI, kg/m2, mean value (SD) | 24.5 ± 5.8 | 24.3 ± 5.8 | 26.4 ± 6.3 | 0.547 | 25.1 ± 5.1 | 22..5 ± 7.7 | 0.245 |
| SAH, n (%) | 54 (63.5) | 47 (55.3) | 7 (8.2) | 0.44 | 41 (48.2) | 13 (15.3) | 0.388 |
| DM, n (%) | 38 (44.7) | 34 (40.0) | 4 (4.7) | 0.695 | 30 (35.3) | 8 (9.4) | 0.98 |
| Sepsis, n (%) | 29 (34.1) | 26 (30.6) | 3 (3.5) | 0.686 | 18 (21.2) | 11 (12.9) | 0.007 |
| Main focus of sepsis: urinary, n (%) | 11 (12.9) | | | | | | |
| Volume eliminated in RRT (mL), mean value (SD) | 1,213.2 ± 1,079 | 1,190 ± 1,087 | 1,612 ± 949 | 0.446 | 1,262.4 ± 1,172.5 | 1022.7 ± 585.3 | 0.272 |
| **Laboratories** | | | | | | | |
| Urea, mean value (SD) | 145.3 ± 69.6 | 147.1 ± 70.7 | 127.2 ± 59.5 | 0.433 | 143.5 ± 73.7 | 151.2 ± 55 | 0.646 |
| <50 mg/dL, n (%) | 8 (9.4) | | | | | | |
| >50 mg/dL, n (%) | 66 (77.6) | | | | | | |
| Creatinine (mg/dL), mean value (SD) | 4.6 ± 1.9 | 4.6 ± 1.8 | 4.8 ± 2.1 | 0.840 | 4.7 ± 1.8 | 4.2 ± 2.0 | 0.378 |
| < 1.2 mg/dL, n (%) | 1 (1.2) | | | | | | |
| > 1.2 mg/dL, n (%) | 72 (84.7) | | | | | | |
| Sodium (mEq/L), mean value (SD) | 137.2 ± 18.1 | 137.1 ± 18.9 | 138 ± 8.2 | 0.815 | 136.7 ± 20.1 | 138.7 ± 9.8 | 0.576 |
| 136 – 145 mg/dL, n (%) | 32 (37.6) | | | | | | |
| <136 or >145 mg/dL, n (%) | 41 (48.2) | | | | | | |
| Potassium (mmol/L), mean value (SD) | 4.7 ± 1.0 | 4.7 ± 1.1 | 4.8 ± 0.9 | 0.842 | 4.7 ± 1.1 | 4.9 ± 0.7 | 0.486 |
| 3.5 to 5.0 mg/dL, n (%) | 42 (49.4) | | | | | | |
| <3.5 or >5.0 mg/dL, n (%) | 31 (36.5) | | | | | | |
| Magnesium (mg/dL), mean value (SD) | 2.1 ± 0.4 | 2.1 ± 0.5 | 1.9 ± 0.2 | 0.074 | 2.1 ± 0.5 | 2.1 ± 0.4 | 0.999 |
| 1.7 to 2.6 mg/dL, n (%) | 40 (47.1) | | | | | | |
| <1.7 or >2.6 mg/dL, n (%) | 12 (14.1) | | | | | | |
| CRP (mg/dL), median (P25; P75) | 146.2 (60.4 - 277.5) | 182.9 ± 150 | 148.8 ± 140.8 | 0.652 | 188 ± 156.2 | 149.3 ± 116.9 | 0.306 |
| PCAL (ng/mL), median (P25; P75) | 2.6 (2.2 - 20.3) | | | | 12.6 ± 13.5 | 1.7 ± 0.7 | 0.018 |
| Leukocytes (/mm3), median (P25; P75) | 12065 (8,292.5 – 17,147.5) | 13872.2 ± 7767.7 | 12284.3 ± 3713.8 | 0.899 | 13667.6 ± 7329.8 | 13868.1 ± 8131.0 | 0.916 |
| 4,500 to 11,000 mm3, n (%) | 28 (32.9) | | | | | | |
| > 11,000 mm3, n (%) | 40 (47.1) | | | | | | |
| Neutrophils (%), median (P25; P75) | 85 (74.8 - 90) | 82.6 ± 10.9 | 74.9 ± 14.1 | 0.126 | 82.7 ± 11.6 | 78.6 ± 10.2 | 0.176 |
| 41 to 77%, n (%) | 20 (23.5) | | | | | | |
| > 77%, n (%) | 50 (58.8) | | | | | | |
| Rods (%), median (P25; P75) | 15.5 (6.8 - 27.3) | 19.3 ± 15.1 | 14 ± 11.8 | 0.313 | 19.0 ± 15.9 | 18.1 ± 11.2 | 0.796 |
| 5 to 11%, n (%) | 21 (24.7) | | | | | | |
| > 11%, n (%) | 40 (47.1) | | | | | | |
| Eosinophils (%), median (P25; P75) | 1 (0 - 3) | 2.2 ± 0.4 | 3.3 ± 0.2 | 0.021 | 2.1 ± 3.9 | 2.9 ± 3.2 | 0.113 |
| 1 to 8%, n (%) | 32 (37.6) | | | | | | |
| > 8%, n (%) | 6 (7.1) | | | | | | |

Abbreviations: Drug-Related Problems (DRPs); Body Mass Index (BMI), Systolic Arterial Hypertension (SAH); Diabetes Mellitus (DM); C-Reactive Protein (CRP); procalcitonin (PCAL); hemodialysis (HD); kilogram per square meter (km/m2); milligram per deciliter (mg/dL); milliequivalent per liter (mEq/L); millimoles per liter (mmol/L); grams per deciliter (g/dL); nanogram per liter (ng/L); per cubic millimeter (/mm3); mililiter (mL).

**Table 2**. Profile of the antimicrobials prescribed to the patients included in the study and distribution according to the drug-related problem (n=85)

| Class | Total (n=85) | DRP | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Error in the prescription | Y incompatibility | Inadequate dosage | Inadequate dose | Drug interaction | Wrong administration of medication | Duplicity |
| Carbapenems | 30(13.7) | 42 (12.8) | 9 (8.8) | 27 (30.7) | 23 (27.1) | 0 (0) | 11 (26.2) | 0 (0) |
| Gluco/ Lipopeptydes | 24(11.0) | 33 (10.1) | 7 (6.9) | 16 (18.2) | 10 (11.8) | 0 (0) | 2 (4.8) | 0 (0) |
| Penicilines | 23(10.5) | 34 (10.4) | 24 (23.5) | 4 (4.5) | 18 (21.2) | 0 (0) | 9 (21.4) | 0 (0) |
| Polymyxins | 21(9.6) | 31 (9.5) | 5 (4.9) | 5 (5.7) | 5 (5.9) | 0 (0) | 0 (0) | 0 (0) |
| Antifungals | 20(9.1) | 27 (8.2) | 8 (7.8) | 3 (3.4) | 2 (2.4) | 24 (30.0) | 4 (9.5) | 0 (0) |
| Others | 19(8.7) | 33 (10.1) | 26 (25.5) | 5 (5.7) | 2 (2.4) | 4 (5.0) | 2 (4.8) | 0 (0) |
| Cephalosporins | 17(7.8) | 29 (8.8) | 5 (4.9) | 2 (2.3) | 2 (2.4) | 0 (0) | 1 (2.4) | 2 (100) |
| Aminoglycosides | 16(7.3) | 17 (5.2) | 1 (1.0) | 9 (10.2) | 9 (10.6) | 2 (2.5) | 2 (4.8) | 0 (0) |
| Macrolides | 11(5.0) | 22 (6.7) | 7 (6.9) | 0 (0) | 0 (0) | 3 (3.8) | 1 (2.4) | 0 (0) |
| Anti-retrovirals | 10 (4.6) | 18 (5.5) | 0 (0) | 2 (2.3) | 3 (3.5) | 11 (13.8) | 3 (7.1) | 0 (0) |
| Fluoroquinolones | 9(4.1) | 16 (4.9) | 3 (2.9) | 7 (8.0) | 3 (3.5) | 17 (21.3) | 1 (2.4) | 0 (0) |
| Antivirals | 7(3.2) | 9 (2.7) | 7 (6.9) | 5 (5.7) | 5 (5.9) | 0 (0) | 2 (4.8) | 0 (0) |
| Antiparasitic | 6(2.7) | 10 (3.0) | 0 (0) | 1 (1.1) | 3 (3.5) | 8(10.0) | 2 (4.8) | 0 (0) |
| Oxazolidinones | 4(1.8) | 3 (0.9) | 0 (0) | 2 (2.3) | 0 (0) | 6 (7.5) | 1 (2.4) | 0 (0) |
| Antimycobacterials | 2(0.9) | 4 (1.2) | 0 | 0 (0) | 0 (0) | 5 (6.3) | 1 (2.4) | 0 (0) |
| Total | 219 (100) | 328 (100) | 102 (100) | 88 (100) | 85 (100) | 80 (100) | 42 (100) | 2 (100) |

Relative frequency among the antimicrobials, n (%). DRPs: Drug-Related Problems.

**Table 3.** Profile of the errors detected in the prescriptions of the patients included in the study (n=85)

| Error in the prescription | n (%) |
|---|---|
| Missing information (dilution and infusion time) | 298 (90.9%) |
| Wrong dilution | 16 (4.9%) |
| Missing supplemental dose | 7 (2.1%) |
| Wrong infusion time | 7 (2.1%) |
| Total | 328 (100) |

As for the NOMs, the median of the total probable negative outcomes associated with the use of antimicrobials detected by patients included in the study was 6.0 (4-11), (minimum 1, maximum 32), where those with the highest frequency were quantitative insecurity (50.6%), non-quantitative insecurity (19.9%) and quantitative ineffectiveness (19.0%) (Table 4). The most prescribed antimicrobials (meropenem, teicoplanin and piperacillin + tazobactam) were related to quantitative insecurity mainly due to prescription errors (lack of dilution information), inadequate dosage or inadequate dose. Piperacillin + tazobactam was the main antimicrobial related to non-quantitative insecurity due to Y incompatibility. Both meropenem and piperacillin + tazobactam were involved in quantitative ineffectiveness due to the lack of information on the infusion time. Table 4. Profile of the problems related to antimicrobial drugs and the probable negative outcomes observed in the patients included in the study (n=85)

**Table 4**. Profile of the problems related to antimicrobial drugs and the probable negative outcomes observed in the patients included in the study (n=85)

| Type of DRP | Type of NOM | | | | | | Total n (%) | Median (P25; P75) per patient |
|---|---|---|---|---|---|---|---|---|
| | Quantitative insecurity | Non-quantitative insecurity | Quantitative ineffectiveness | Non-quantitative ineffectiveness | Effect of unnecessary medication | Untreated health problem | | |
| Error in the prescription | 156 | 0 | 137 | 35 | 0 | 0 | 328 (45.1) | 4 (2.0-5.0) |
| Y incompatibility | 0 | 102 | 0 | 0 | 0 | 0 | 102 (14.0) | 0 (0.0-2.0) |
| Inadequate dosage | 88 | 0 | 0 | 0 | 0 | 0 | 88 (12.1) | 1 (0.0-2.0) |
| Inadequate dose | 85 | 0 | 0 | 0 | 0 | 0 | 85 (11.7) | 1 (0,0-2.0) |
| Drug interaction | 37 | 39 | 1 | 3 | 0 | 0 | 80 (11.0) | 0 (0.0-1.0) |
| Wrong administration of medication | 0 | 2 | 0 | 40 | 0 | 0 | 42 (5.8) | 0 (0.0-1.0) |
| Duplicity | 2 | 0 | 0 | 0 | 0 | 0 | 2 (0.3) | 0 (0.0-0.0) |
| Total | 368 (50.6) | 145 (19.9) | 138 (19.0) | 76 (10.5) | 0 (0) | 0 (0) | 727 (100) | 6.5 (4.0-11,0) |

## Discussion

The sociodemographic and clinical profile observed in the patients in this study was similar to that of the Brazilian Chronic Dialysis Survey 2017, in which the majority were male, the age group from 45 to 64 years old represented 42.6% of the patients and whose underlying primary diseases were hypertension (34%) and diabetes (31%)[1].

In the study by Silva et al. (2017), a similar sociodemographic profile was also found (63% of male gender and an age frequency of 34.8% between 66 and 80 years old); however, the frequency of sepsis (17.3 %) was lower than that found in this study (34.1%). Although the patients of Silva et al. are not kidney patients, they are critical patients[9].

Sepsis is the leading cause of acute kidney injury in critically ill patients, and half of these patients require RRT[10,11]. Thus, the adoption of measures that lead to decreased mortality and costs associated with treatment and hospitalization is important. The actions with the greatest impact include the early administration of antimicrobials, the choice of which is based on the patient's history, recent use of ATM and the source of pathogens (community or hospital)[12]. In this study, most patients on RRT used antimicrobials to treat sepsis (n=29; 34.9%).

The empirical use of antibiotic therapy is essential for a good prognosis of the patient. Before administration, it is important to perform cultures to identify the etiologic agent of the infection, thus being able to adapt the antibiotic therapy to cover pathogens resistant to the initial empirical scheme or to de-escalate the antimicrobial from the empirical therapy, reducing the cost of treatment, diminishing the side effects, and avoiding bacterial resistance[13]. In this study, 29.4% of the patients were using antimicrobials for empirical treatment of pneumonia not associated with mechanical ventilation and only 16.5% used antimicrobials guided by culture results. Despite the frequency of empirical treatments being high, due to the fact that this is a cross-sectional study conducted in a single day of observation, it was not possible to evaluate the NOMs of effect of unnecessary medication and untreated health problem because, to assess them it would be necessary to observe the de-escalation or fitness of the antibiotic therapy to cover resistant agents, which would require more evaluation days.

In the study by Fideles et al. (2015), anti-infectives were the class of drugs with the most pharmaceutical recommendations, with meropenem (7.3%), teicoplanin (11.9%), piperacillin/tazobactam (4.2%) and polymyxin B (5.6%) being the most prevalent14. Although that study is not specifically about ATMs and in dialysis patients, like this one, the profiles of antimicrobials with more DRPs were similar to those from this study. Systemic anti-infectives have also been found to be the class most involved in problems related to antimicrobial drugs in critically ill patients in an intensive care unit, thus demonstrating the importance of in-depth studies in this class of drugs[9].

Regarding drug-related problems in patients on RRT, there is a dearth of publications, especially with regard to antimicrobials. However, like in this study, Aguiar et al. (2006) demonstrated a high percentage of errors in the prescriptions, mainly the lack of prescription of the diluent (61.5%)15. Another study that found lack of information in the prescription (dilution and infusion time) as one of the drug-related problems most frequent was Silva et al. 2017 (33.2%), presenting an antimicrobial profile similar to the one observed in this study[9].

Detecting errors in the prescriptions is of great importance, since the lack of correct information in the prescription can have serious consequences for the patients. With regard to antimicrobials, the absence of the dilution and the infusion time can influence therapeutic efficacy. Studies of pharmacokinetics/pharmacodynamics (pK/pD) evidenced the impact of the serum levels and of the response to antimicrobials. It is known that the effectiveness of an antimicrobial can be time-dependent (related to the time of exposure to a minimum inhibitory concentration), dependent on a specific concentration (where it has to reach the maximum inhibitory concentration) or dependent on the concentration and time. Therefore, it is important that a prescription contains, in addition to the dose, the infusion time so as not to influence the effectiveness of this medication[16]. Studies have shown that carbapenems, such as meropenem, in prolonged infusion for 3 hours demonstrate superiority in pK/pD and lower chances of adverse events[17].

Another problem caused by the lack or omission of information in the prescription is the ADRs, such as the red man syndrome, caused by the rapid infusion of vancomycin. This should be infused in 60 minutes for a dose of up to 1g, or in more than 60 minutes for larger doses. This syndrome can cause everything from flushing or itching to severe reactions, such as muscle spasm, chest pain or hypotension, which can be pre-treated with antihistamines combined with an H2 receptor blocker. Therefore, it is essential that the medical prescription contains all the necessary information in order to guarantee the safe use of medications[18].

The concomitant use of medications is a frequent situation when patients need fluid restriction, are in palliative care or if there is a clinical need for multiple medications administered in a short period of time. Infusion through the same access of different medications, when essential to meet the patient's needs, should never be performed at the convenience of the health professional because, although there is little information available about the occurrence of serious events caused by medication incompatibilities, this lack of notification may be due to the fact that the adverse effects caused by drug incompatibilities are difficult to identify in seriously ill patients[19].

Drug incompatibilities via Y-connection are physical or chemical reactions between drugs, when simultaneous administration by the same route occurs, which can compromise therapeutic effectiveness and safety. These physical-chemical reactions can cause precipitation, separation, gas formation and changes in color or turbidity. This can result in catheter occlusion or emboli formation, causing organ failure and death. These reactions are usually detectable through a visual check. Among the chemical reactions, oxidation, reduction and hydrolysis may occur, which may result in loss of potency or the formation of toxic by-products[19].

In the study by Araujo and collaborators (2017), 506 pharmaceutical interventions were performed (mean values of 51 interventions/month and 1.7 interventions/day), and the most prevalent pharmaceutical intervention was drug incompatibility via Y-connection (n=171; 38.4%), which causes therapeutic failure or ineffectiveness[20]. In the present study, drug incompatibility via Y-connection was the second most frequent problem related to antimicrobial drugs (14.1%), and the difference in prevalence may be due to the type of study, the profile of patients included and the place of performance.

As this is a retrospective study, the wrong administration of the medication was evaluated based on the error in the medication schedule. As Carvalho et al. (2017) quote in their book, in order to avoid possible interferences in the metabolization of dialysable drugs and so that they are not eliminated because of an administration performed just before or during the dialysis period, the correct scheduling is essential[3]. Oliveira (2017) analyzed the pharmacokinetics of two dialysable drugs in patients undergoing renal replacement therapy: meropenem and vancomycin. This study found that meropenem had a mean clearance of 78% and that vancomycin had a mean of 41% in patients undergoing low-efficiency extended dialysis [21]. Thus, if these antimicrobials are not administered after RRT, therapeutic failure may occur with the possibility of bacterial resistance.

The pharmacokinetics of antimicrobials can be altered by several mechanisms in critically ill patients. In sepsis, absorption, distribution and elimination are altered due to the clinical condition. There is an increase in renal perfusion and of creatinine clearance, leading to an increased elimination of hydrophilic drugs, as well as optimization of other metabolism and elimination ways, causing a reduction in the serum concentration of hydrophilic antimicrobials. With the progression of sepsis and organ dysfunction, there is myocardial depression and decreased organic perfusion, leading to decreased antimicrobial ***clearance***, increased half-life and potential toxicity, increasing the serum concentration of the drug and/or accumulation of its metabolites[22].

Therefore, in addition to scheduling, dose adjustment of antimicrobials in patients with RRT is of paramount importance. Such is the case of vancomycin, which, due to its narrow therapeutic margin, exposes the patient to a high risk of toxicity and significant pharmacotherapeutic variations or to bacterial resistance[23]. This vancomycin toxicity can cause adverse effects, such as urticaria, exfoliative dermatitis, macular rashes, eosinophilia, vasculitis, anaphylaxis, vascular collapse, nephrotoxicity and ototoxicity, and can be irreversible[24].

As previously mentioned, no studies were found on problems related to antimicrobial drugs and NOMs in a population similar to that included in this study. However, in a recent study D'agata and collaborators (2018) evaluated the impact of an antimicrobial management program in outpatient hemodialysis centers. This quasi-experimental study (12 months pre-intervention versus 12 months post-intervention) had the following actions: support meetings for the centers' leadership; educational programs with multi-professional staff from the centers; video conferences with leadership, researchers and infectologists to discuss cases, among others. At the end, a 6% monthly reduction in the antimicrobial doses was achieved per 100 patient-month with p=0.02, with no negative outcomes[25].

The main limitation is the fact that this study is observational, making it impossible to establish a causal relationship between the variables. The negative outcomes detected were analyzed in relation to the potential for damage, without confirmation of damage to the patient. However, they provide relevant information on the use of antimicrobials in dialysis patients, particularly in hospitalized ones.

## Conclusion

Patients undergoing renal dialysis and antimicrobial therapy in this study had at least 1 (one) problem related to antimicrobial drugs and, consequently, 1 (one) probable NOM. The main problem observed was the error in the prescription, which can be avoided with the performance of the multi-professional team, in order to detect and prevent problems through the implementation of computerized systems, continuing education, manuals, protocols and routines for safe prescription, coupled with the implementation of an antimicrobial stewardship program. These measures could prevent the main NOMs observed, insecurity and quantitative ineffectiveness, bringing benefits to patients' health and preventing bacterial resistance.

**Funding**

This research was not funded by any institution or company.

**Collaboration of the authors**

CCMS and EAMD conceived the project; CCMS collected the data; CCMS and EAMD analyzed and interpreted the data; EAMD performed the statistical analysis of the data; CCMS and EAMD drafted and critically reviewed the article. The authors were responsible for all the aspects of the work in ensuring the accuracy and integrity of any part of the paper.

**Conflict of interests**

The authors declare no conflicts of interests in this paper.

## References

1. Thomé FS, Sesso RC, Lopes AA, ***et al***. Inquérito brasileiro de diálise crônica 2017. Brazilian Journal of Nephrology. 2019; (2): 208-214.

2. Cruz CGR, Oliveira SC, Matsui T. Curso de especialização profissional de nível técnico em enfermagem: Livro do aluno terapia renal substitutiva, 1°ed. São Paulo. FUNDAP. 2012: 205p

3. Carvalho DCMF, Barbosa LMG, Almeida IM, ***et al***. Manual de farmácia clínica e cuidado ao paciente, 1°ed. Rio de Janeiro, Editora Atheneu, 2017: p. 237-249.

4. Brasil. Ministério da saúde. Agência Nacional de Vigilância Sanitária. Uso de antimicrobianos em populações especiais: insuficiência renal, 2008. Disponível em: http://www.anvisa.gov.br/servicosaude/controle/rede_rm/cursos/atm_racional/modulo4/insu_renal.htm. Acess in August 1st 2018.

5. Hernández DS, Castro MMS, Dáder MJF. Método Dáder: Manual de seguimento farmacoterapêutico, 3°ed. Alfenas, Editora Universidade Federal de Alfenas, 2014: 128 p.

6. Aizenstein ML, Tomassi MH. Problemas relacionados a medicamentos; reações adversas a medicamentos e erros de medicação: a necessidade de uma padronização nas definições e classificações. Revista de Ciências Farmacêuticas Básica e Aplicada. 2011; 32(2): 169-173.

7. Gilbert DN, Chambers HF, Eliopoulos GM, ***et al***. Guia Sanford para terapia antimicrobiana 2017, 47ª ed. Rio de Janeiro, Guanabara Koogan, 2017: 258.

8. Brasil. Ministério da saúde. Agência Nacional de Vigilância Sanitária. Protocolo de segurança na prescrição, uso e administração de medicamentos, 2013. Disponível em: https://www20.anvisa.gov.br/segurancadopaciente/index.php/publicacoes/item/seguranca-na-prescricao-uso-e-administracao-de-medicamentos. Acess in August 1st 2018.

9. Silva ACS, Sousa DSC, Perraud EBC, ***et al***. Acompanhamento farmacoterapêutico em unidade de terapia intensiva respiratória: descrição e analise de resultados. Publicação Oficial do Instituto de Ensino e Pesquisa Albert Einstein. 2017; 16(2): 1-7.

10. Davenport A. Dialytic treatment for septic pacients with acute kidney injury. Kidney Blood Pressure Research. 2011; 34(1): 218-224.

11. Zarjou A, Agarwal A. Sepsis and acute kidney injury. Journal American Society Nephrology. 2011; 22(1): 999–1006.

12. Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in critically ill patient. Critical Care Medicine. 2009; 37(3): 840-851.

13. Diament D, Salomão R, Rigatto O, ***et al***. Diretrizes para tratamento da sepse grave/choque séptico – abordagem do agente infeccioso – diagnóstico. Revista Brasileira de Terapia Intensiva. 2011; 23(2): 134-144.

14. Fideles GMA, Alcântra-Neto JM, Peixoto-Júnior AA, ***et al***. Recomendações farmacêuticas em unidades clínicas. Revista Brasileira de Terapia Intensiva. 2015; 27(2): 149-154.

15. Aguiar G, Júnior LAS, Ferreira MAA. Ilegibilidade e ausência de informação nas prescrições médicas: fatores de risco relacionados a erros de medicação. Revista Brasileira de Pesquisa em Saúde. 2006; 19(2): 84-91.

16. Zamoner W, De Freitas FM, Garms DSS, ***et al***. Pharmacokinetics and pharmacodynamics of antibiotics in critically ill acute kidney injury patients. Pharma Research & Perspectives. 2016; 4(6): 1-7.

17. Simonato BS, Teixeira GC, Rebecca ESW, ***et al***. Infusão contínua versus intermitente de meropenem na prática clínica. Arquivos de Ciências da Saúde da UNIPAR. 2017; 21: 59-64.

18. Drisyamol KA, Mahesh NM. Vancomycin induced red man syndrome. International Journal of Pharmacological Research. 2016; 6(4): 127-132.

19. Bentley J, Heard K, Collins G, ***et al***. Mixing medicines: how to ensure patient safety. The Pharmaceutical Journal. 2015; 294(7859): 453-456.

20. Araujo EO, Viapiana M, Domingues EAM, ***et al***. Intervenções farmacêuticas em uma unidade de terapia intensiva de um hospital universitário. Revista Brasileira de Farmácia Hospitalar e Serviços de Saúde. 2017; 8(3): 25-30.

21. Oliveira MS. Avaliação farmacocinética e farmacodinâmica de meropenem e vancomicina em pacientes submetidos à diálise estendida de baixa eficiência (SLED) [Tese de doutorado]. Faculdade de Medicina da Universidade de São Paulo, São Paulo, 2017.

22. Freitas FM, Zamoner W, Garms DSS, ***et al***. O uso de antimicrobianos em pacientes sépticos com lesão renal aguda. Jornal Brasileiro de Nefrologia. 2017; 39(3): 323-328.

23. Santos AB, Duarte A, Saião AS. Vancomycin in clinical practice – a review. Jornal de Investigação Biomédica e Biofarmacêutica. 2011; 8(2): 321-327.

24. Vieira JPG. Avaliação do impacto da monitorização farmacocinética clínica da vancomicina nos outcomes clínicos de doentes internados [Tese de mestrado]. Faculdade de Farmácia da Universidade de Coimbra, Coimbra, 2016.

25. D'agata EMC, Lindberg CC, Lindberg CM, ***et al***. The positive effects of an antimicrobial stewardship program targeting outpatient hemodialysis facilities. Infection Control & Hospital Epidemiology. 2018; 39(12): 1400-1405.