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ORIGINAL ARTICLE

Evaluation of the Pharmacotherapy Complexity Index in Patients of a Renal Transplant Clinic

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Abstract: **Objective:** To evaluate the complexity of pharmacotherapy of kidney transplant patients in an outpatient clinic in the Brazilian Central-West region. **Methods:** This is a study that respects a descriptive cross-sectional design to evaluate the complexity index of pharmacological treatment through the documentary analysis of medical records. To calculate this index, the patient's continuous use medications were considered, and the Pharmacotherapy Complexity Index (PCI) was adopted. To determine the PCI classification ranges, analysis of a larger group of patients (significant sample) was performed, and the quartiles of the PCI results were adopted. A pilot sample was used to describe the influence of drugs on PCI. **Results:** A total of 247 patients were included in the study to define the strata of treatment complexity. The PCI in the sample ranged from 10 to 83.5, and, by quartile analysis, up to 22.5 was considered low complexity, between 22.6 and 27.0 medium complexity, between 27.1 and 36.0 high complexity, and above 36.1 very high complexity. The case study for the PCI evaluation occurred with 20 patients and demonstrated that the complexity is not defined by the immunosuppressive treatment, but by the drugs used for the underlying diseases or the health problems arising from age and immunosuppression (comorbidities). Diabetes mellitus appears as the disease that contributes the most to complexity through the use of insulins. **Conclusion:** Patients with a higher number of drug doses and with conditions dependent on insulin therapy associated with immunosuppressive pharmacotherapy are the most complex and demand greater need for follow-up because of the difficulties faced in treatment.

Descriptors: Kidney Transplantation; Drug Use; Immunosuppression.

INTRODUCTION

Kidney transplantation is a proposed therapy for patients with end-stage chronic kidney disease (CKD) that improves quality of life, reduces mortality, and increases life expectancy when compared to other treatments, such as dialysis.[1,2] After the transplant, or even immediately before, it is necessary for the individual to start immunosuppressive pharmacotherapy, which aims to prevent graft rejection.[3]

Besides immunosuppressive pharmacotherapy, which is fundamental for a good prognosis, the patient must continue to use the medications he or she was already using to control other conditions, such as underlying diseases or others diagnosed after the transplant, in which metabolic diseases stand out. Proper use of all medications contributes to the best prognosis.[4]

The complexity of the treatment, however, can lead to nonadherence to pharmacotherapy, which is common and affects 36 to 55% of kidney transplant

patients. Thus, using adherence measures, recognizing the reasons that lead the patient not to comply with the treatment, and thus performing the appropriate intervention to modify this picture is a necessary clinical conduct with regard to these patients. However, for these interventions to be effective, the complexity of the treatments must be understood, since adherence to post-transplant pharmacotherapy involves several aspects, from those inherent to the individual, to the environment in which they live and its social aspects.[5]

The complexity of a treatment must be considered by several factors, such as the pharmaceutical form of the drugs used, the frequency of doses, and the quantity of drugs prescribed.[6] One of the strategies to assess this complexity is the (Pharmacotherapy Complexity Index (PCI), which is an instrument with high specificity, originally developed in English and later translated by Melchiors et al. into Portuguese.[7] It is divided into three sections: information about the dosage form; dosage frequency; and additional information, such as use with food or the need to break pills. The scoring of the sections is given by analyzing the patient's prescription, and the complexity index, obtained by adding up the scores of the three sections.[7] For transplant patients, the index has been used in a timely manner.[8]

In this sense, the objective of this study was to evaluate the complexity of the pharmacological treatment of kidney transplant patients seen at the outpatient clinic of the University Hospital of Brasília in order to make the health team aware of this factor.

METHODS

A cross-sectional study was developed based on the analysis and evaluation of medical records of kidney transplant patients seen at an outpatient clinic in Brasília. It was divided into two stages: the first with emphasis on identifying the strata for the PCI classification; and the second, for the case study description.

The study population refers to kidney transplant patients, and the sampling process was done by convenience among the available medical records in the two stages. At the time of data collection (2021), the service had about 350 registered patients, considering a 5% error, 95% confidence interval, and a prevalence of use of other medications besides immunosuppression of 50%, which maximizes the sample. The minimum number of records to be observed was 184; however, in the first stage, 247 records were evaluated to calculate the PCI and its strata (quartiles).

Subsequently, 20 patients were selected, according to the strata of the complexity index, for the case study.

In the stage of determining the PCI strata, pharmacotherapy data were collected based on the last doctor's visit, and it was necessary to collect information about the pharmaceutical form, dose, and dosage. Furthermore, additional information about medication use, such as the need to associate it with diet, was also investigated. The information collected from the patients' profile was age, gender, time since transplant, and diagnosis of other diseases besides renal failure.

The PCI calculation has three steps, which are divided into sections as follows:

- Section A: the pharmaceutical forms (dosage forms);
- section B: the dosage (dose frequency);
- section C: additional information for correct use (further instructions).

In this calculation, the instrument translated and validated into Portuguese by Melchiors et al.[7]

The data were organized in spreadsheet format in the software Excel, in which a descriptive analysis was performed. The complexity was classified using the total sample of patients (247) and organized in quartiles: first quartile (0-25%), considered low; second quartile (25.1-50%), medium; third quartile (50.1-75%), high; and last quartile (75.1-100%), very high.

Then convenience selection was made of five patients in each of the strata, which totaled 20 patients for case studies. During the descriptive analysis of these patients, a description of all the medications in use and characteristics, such as pharmaceutical form, number of doses, and dosage, was sought, in addition to the age and PCI stratum to which each one belonged. For the case study patients, it was possible to present the partial complexity index (only for immunosuppressants), in addition to the total complexity index, in this case taking into account all the drugs being used.

To analyze the influence of the complexity of immunosuppressants with the other drugs in use in the treatment of the kidney transplant patient, the normality of the total and partial complexities (only for immunosuppressants and for the other drugs) was initially evaluated. For this, the Shapiro-Wilk test was adopted, and $p < 0.05$ was observed, which shows that the distribution does not respect normality. In this sense, for the comparison of the medians observed for complexity, the Kruskal-Wallis test was adopted, considering $p < 0.05$ as a significant value.

For the drugs described in the case study, the classification of the Anatomical Therapeutic Chemical was adopted.[9]

The project was written according to the ethical recommendations of Resolution No. 466/12, of the National Health Council, and approved by the Research Ethics Committee, with Opinion No. 3,033,663.

RESULTS

A total of 247 kidney transplant patients were included in the study, with half of the transplants having taken place by 2014. Of the 247 patients enrolled, only 96 (38.4%) are women, and the time to transplant ranged from 0 to 19 years. According to the medical records, in addition to kidney failure, the patients have other diseases, with a median of 3, and up to 13 other health problems. As for the number of medications in use, a minimum of 3 and a maximum of 23 (median = 8) were observed. The PCI showed values between 10 and 83.5, and the strata are shown in Table 1.

To identify the drugs that contribute most to the complexity of treatment, a case description of a sample of patients was performed. Table 2 describes the immunosuppressive drugs used for the case study patients, and the partial complexity index (related to immunosuppressants only) is presented. In this case, the Kruskal-Wallis test demonstrated $p = 0.116$ when comparing the median complexity of immunosuppressants for patients classified in the different complexity strata. It is observed, then, that the complexity conferred by the immunosuppressive regimen did not differ significantly between strata.

Table 3 shows the other drugs used by all case study patients individually. These drugs are those used for the treatment of underlying diseases, generally chronic and nontransmissible, and that add greater complexity to the picture, besides drugs related to the treatment protocols of the transplanted patient, such as gastric protectors and antibiotics.

It was observed that, in Table 3, which refers to the nonimmunosuppressive medications used by the patients, those that appear with greater recurrence are those that act on the cardiovascular system, such as amlodipine and atenolol; medications that act on the alimentary system and metabolism, such as insulins and omeprazole; as well as hormones such as levothyroxine. The most frequently used pharmaceutical form was tablets, followed by injectable drugs.

When evaluating the total complexity data using the Kruskal-Wallis test, $p < 0.001$ was observed, demonstrating that complexity increases significantly among the strata. Similarly, when evaluating the influence of the other drugs by also adopting the Kruskal-Wallis test, $p < 0.001$ was found, also identifying significant difference among the strata. In this case, it is the nonimmunosuppressive drugs that contribute significantly to the complexity of the treatments.

DISCUSSION

The results presented allow the observation of PCI behavior influenced by both quantity and pharmaceutical form, dosage, and additional usage guidelines. Patients with higher complexity strata are generally those with larger amounts of medications, which are also subject to higher risks of drug interactions and adverse events.

According to Marienne et al,[8] the complexity of pharmacotherapy tends to decrease soon after transplantation, when it is possible to withdraw some of the prophylactic drugs adopted and when full function of the graft is obtained, which leads to the control of several parameters, including blood pressure. However, even though the aim of this study was not to evaluate the influence of age on treatment complexity, the case study sample showed that younger patients in general have lower PCI compared to older patients, and this is perhaps related to the longer duration of kidney disease and also the prevalence of diseases that have a relationship with aging, however Marianne et al.[8] did not observe a correlation between age of transplantation and PCI in their study.

Through the results of the study, it was possible to observe that the contribution of immunosuppressive treatment to PCI is quite similar in all the patients observed. However, when the patient has other diseases, such as hypertension, dyslipidemia or diabetes, and requires other medications, it has been observed that the PCI increases considerably, often going from a low complexity classification to a high complexity picture. In other words, the choice of immunosuppression is related to the risk of rejection, while additional pharmacotherapy is linked to the patient's other health problems. In this sense, the role of the health care team in patient self-care must be understood, because the use of medications in this group goes beyond adherence

Table 1. Classification of the pharmacotherapy complexity index (PCI) according to the quartiles observed in the sample of renal transplant outpatients (n = 250).

QUARTILE (%)	PCI INTERVAL	CLASSIFICATION
First: 0-25	10-22.5	Low
Second: 25.1-50	22.6-27	Medium
Third: 50.1-75	27.1-36	High
Fourth: 75.1-100	36.1-83.5	Very high

Table 2. Description of immunosuppressants used by kidney transplant recipients and the partial pharmacotherapy complexity index in an outpatient clinic, Central Western Region, 2021.

Patient	Age (Years)	Classification (Total PCI)	Immunosuppressive Drugs	ATC	Number of Doses	Posology	Pharmaceutical Form	Pci (Partial)
P1	36	Low (10)	Sirolimus	L04AA10	1	Once a day	Tablet	5
P2	35	Low (17)	Sirolimus Azathioprine Prednisone	L04AA10 L04AX01 H02AB07	3 1 1	Once a day Once a day Once a day	Tablet Tablet Tablet	13
P3	28	Low (22)	Tacrolimus Azathioprine Prednisone	L04AD02 L04AX01 H02AB07	2 1 2	Twice a day Once a day Once a day	Tablet Tablet Tablet	14
P4	36	Low (19)	Tacrolimus Sodium mycophenolate Prednisone	L04AD02 L04AA06 H02AB07	7 2 1	Twice a day Once a day Once a day	Tablet Tablet Tablet	15
P5	29	Low (13)	Tacrolimus Prednisone Azathioprine	L04AD02 H02AB07 L04AX01	3 1 2	Once a day Once a day Once a day	Tablet Tablet Tablet	13
P6	20	Medium (23)	Tacrolimus Sodium mycophenolate Prednisone	L04AD02 L04AA06 H02AB07	7 2 1 dose	Twice a day Twice a day Once a day	Tablet Tablet Tablet	16
P7	64	Medium (23)	Prednisone Tacrolimus Sodium mycophenolate	H02AB07 L04AD02 L04AA06	1 2 4.0	Once a day Once a day Twice a day	Tablet Tablet Tablet	14
P8	55	Medium (24)	Tacrolimus Sirolimus Prednisone	L04AD02 L04AA10 H02AB07	2 1 1	Twice a day Once a day Once a day	Tablet Tablet Tablet	15
P9	70	Medium (23)	Tacrolimus Sodium mycophenolate Prednisone	L04AD02 L04AA06 H02AB07	6 4.0 1	Twice a day Twice a day Once a day	Tablet Tablet Tablet	14
P10	46	Medium (23)	Tacrolimus Sodium mycophenolate Prednisone	L04AD02 L04AA06 H02AB07	7 4.0 1	Twice a day Twice a day Once a day	Tablet Tablet Tablet	16
P11	49	High (28)	Sodium mycophenolate Sirolimus Prednisone	L04AA06 L04AA10 H02AB07	3 1 1	3 times a day Once a day Once a day	Tablet Tablet Tablet	14
P12	41	High (28)	Tacrolimus Sirolimus Prednisone	L04AD02 L04AA10 H02AB07	3 1 1	Twice a day Once a day Once a day	Tablet Tablet Tablet	15
P13	50	High (30)	Tacrolimus Sodium mycophenolate Prednisone	L04AD02 L04AA06 H02AB07	5 4.0 1	Twice a day Twice a day Once a day	Tablet Tablet Tablet	18
P14	42	High (29)	Sirolimus Sodium mycophenolate Prednisone	L04AA10 L04AA06 H02AB07	1 2 1	Once a day Once a day Once a day	Tablet Tablet Tablet	13
P15	52	High (30)	Tacrolimus Sodium mycophenolate Prednisone	L04AD02 L04AA06 H02AB07	4.0 4.0 1	Once a day Twice a day Once a day	Tablet Tablet Tablet	15
P16	54	Very high (52)	Tacrolimus Sirolimus Prednisone	L04AD02 L04AA10 H02AB07	7 2 1	Twice a day Once a day Once a day	Tablet Tablet Tablet	17
P17	55	Very high (53)	Tacrolimus Sodium mycophenolate Prednisone	L04AD02 L04AA06 H02AB07	2 2 1	Once a day Twice a day Once a day	Tablet Tablet Tablet	14
P18	41	Very high (40)	Tacrolimus Sodium mycophenolate Prednisone	L04AD02 L04AA06 H02AB07	8 3 1	Twice a day 3 times a day Once a day	Tablet Tablet Tablet	16
P19	49	Very high (39)	Tacrolimus Sirolimus Prednisone	L04AD02 L04AA10 H02AB07	3 2 1	3 times a day Once a day Once a day	Tablet Tablet Tablet	15
P20	73	Very high (63)	Tacrolimus Everolimus Prednisone	L04AD02 L04AA18 H02AB07	2 4.0 1	Once a day Twice a day Once a day	Tablet Tablet Tablet	15

ATC: anatomical therapeutic chemical classification; PCI: pharmacotherapy complexity index; total PCI: considering all the drugs in use; partial PCI: considering only the immunosuppressants.

Table 3. Description of nonimmunosuppressive drugs used by kidney transplant patients in an outpatient clinic in the Central-West, Brazil, 2021.

Patient	Age (Years)	Classification (Total Pci)	Other Drugs	Classification Atc	Number of Doses	Posology	Pharmaceutical Form
P1	36	Low (10)	Ezetimibe	C10AX09	1	Once a day	Tablet
P2	35	Low (17)	Cholecalciferol	A11CC05	1	Once a week	Tablet
P3	28	Low (22)	Tamsulosin	G04CA02	1	Once a day	Tablet
			Nitrofurantoin	J01XE01	1	Once a day	Tablet
			Cholecalciferol	A11CC05	1	Once a week	Tablet
P4	36	Low (19)	Cholecalciferol	A11CC05	1	Once a week	Capsule
P5	29	Low (13)	-	-	-	-	-
P6	20	Medium (23)	Amlodipine	C08CA01	2	Twice a day	Tablet
			Microvlar	G03AA07	1	Once a day	Tablet
P7	64	Medium (25)	Levothyroxine 50 mcg	H03AA01	1	Once a day	Tablet
			Levothyroxine 25 mcg	H03AA01	1	Once a day	Tablet
			Atorvastatin	C10AA05	2	Once a day	Tablet
P8	55	Medium (24)	Losartan	C09CA01	1	Once a day	Tablet
			Alopurinol	M04AA01	1	Once a day	Tablet
			Atorvastatin	C10AA05	2	Once a day	Tablet
P9	70	Medium (23)	Atenolol	C07AB03	1	Once a day	Tablet
			Sulfamethoxazole + trimethoprim	J01EE07	1	Once a day	Tablet
P10	46	Medium (23)	Fluoxetine	N06AB03	1	Once a day	Tablet
			Losartan	C09CA01	1	Once a day	Tablet
P11	49	High (28)	Atenolol	C07AB03	4.0	Twice a day	Tablet
			Gliclazide	A10BB09	1	Once a day	Tablet
			Indapamide	C03BA11	1	Once a day	Tablet
			Cholecalciferol	A11CC05	1	Once a week	Capsule
P12	41	High (28)	Clonidine	C02AC01	2	Twice a day	Tablet
			Amlodipine	C08CA0	1	Once a day	Tablet
			Atenolol	C07AB03	2	Twice a day	Tablet
P13	50	High (30)	Carvedilol	C07AG02	4.0	Twice a day	Tablet
			Sulfamethoxazole + trimethoprim	J01EE07	1	Once a day	Tablet
			Amlodipine	C08CA01	2	Once a day	Tablet
P14	42	High (29)	Losartan	C09CA01	2	Twice a day	Tablet
			Furosemide	C03CA01	1	Once a day	Tablet
			Cinacalcet hydrochloride	H05BX01	1	Once a day	Tablet
			Atenolol	C07AB03	1	Once a day	Tablet
			Simvastatin	C10AA01	1	Once a day	Tablet
P15	52	High (30)	Omeprazole	A02BC01	2	Twice a day	Tablet
			Furosemide	C03CA01	1	Once a day	Tablet
			Hydrochlorothiazide	C03AA03	1	Once a day	Tablet
			Sulfamethoxazole + trimethoprim	J01EE07	1	Once a day	Tablet
			Magnesium chloride	A12CC01	1	Once a day	Tablet
P16	54	Very high (52)	Omeprazole	A02BC01	1	Once a day	Tablet
			Regular insulin	A10AC	10 IU	3 times a day	Injection
			NPH insulin	A10AD	18 IU/10	2 /1 times a day	Injection
			Furosemide	C03CA01	2	Twice a day	Tablet
			Sulfamethoxazole + trimethoprim	J01EE07	1	Once a day	Tablet
			Clonidine	C02AC01	2	Twice a day	Tablet
P17	55	Very high (53)	Omeprazole	A02BC01	1	Once a day	Tablet
			Insulin glargine	A10AE	10 IU	3 times a day	Injection
			Ultra-rapid insulin	A10AB	5 IU	3 times a day	Injection
			Atenolol	C07AB03	2	Twice a day	Tablet
			Amlodipine	C08CA01	2	Twice a day	Tablet
			Hydrochlorothiazide	C03AA03	1	Once a day	Tablet
			Acetylsalicylic acid	B01AC06	1	Once a day	Tablet
			Losartan	C09CA01	1	Once a day	Tablet
P18	41	Very high (40)	Levothyroxine	H03AA01	2	Once a day	Tablet
			Ultra-rapid insulin	A10AB	1 IU	3 times a day	Injection
			Lantus insulin	A10AE	24 IU	Once a day	Injection
			Sulfamethoxazole + trimethoprim	J01EE07	1	Once a day	Tablet

Continue...

Table 3. Continuation.

Patient	Age (Years)	Classification (Total Pci)	Other Drugs	Classification Atc	Number of Doses	Posology	Pharmaceutical Form
P19	49	Very high (39)	Omeprazole	A02BC01	1	Once a day	Tablet
			NPH insulin	A10AD	19 IU	Once a day	Injection
			Amlodipine	C08CA01	2	Twice a day	Tablet
			Regular insulin	A10AB01	16 IU	Twice a day	
P20	73	Very high (63)	Levothyroxine	H03AA01	1	Once a day	Tablet
			NPH insulin	A10AD	16 IU	Twice a day	Injection
			Regular insulin	A10AC	10 IU	Twice a day	Injection
			Artrolive	M01AX05	2	Twice a day	Tablet
			Losartan	C09CA01	2	Twice a day	Tablet
			Amlodipine	C08CA01	2	Twice a day	Tablet
			Sertraline	N06AB06	1	Once a day	Tablet
			Acetylsalicylic acid	B01AC06	1	Once a day	Tablet
			Furosemide	C03CA01	2	Twice a day	Tablet
			Simvastatin	C10AA01	1	Once a day	Tablet

ATC: anatomical therapeutic chemical classification; NPH: neutral protamine Hagedorn; PCI: pharmacotherapy complexity index; total PCI: considering all the drugs in use; partial PCI: considering only the immunosuppressants; IU: international units.

to immunosuppressive medication, as evaluated in many studies.[10] In addition, such adherence can be influenced by a variety of conditions and actors, which demonstrates a scenario with many interfering factors.[11] Moreover, the polypharmacy, to which many patients are submitted, can influence the reduction in the quality of life of these individuals.[8]

Among the most frequently used nonimmunosuppressive drugs are those related to the cardiovascular system, whether for pressure control or for the management of dyslipidemia. Cardiac comorbidities, when observed in patients who already have diagnoses for other chronic diseases, further complicate the clinical management and make treatment compliance more difficult.[12] For these patients, complexity was found to be related in a special way to the number of medications and daily doses administered.

In patients with very high PCI, frequent use of insulins was observed. Injectable drugs, according to Melchiors et al,[7] make treatment more complex because of the difficulty of administration. It is worth noting that in addition to pretransplant diabetes, there is the possibility of up to 27% of patients developing diabetes after transplantation. This diabetes behaves like type 2 diabetes, but often evolves rapidly to the need for the use of insulins, a situation that, added to that of those patients with type 1 diabetes, makes the use of this class of drugs very common. Their contribution to the complexity of pharmacotherapy by the health care team should always be considered.[12]

This increased complexity may also impact adherence to immunosuppressive treatment. The negative impact of nonadherence to treatment has been documented and is associated with increased rejection of the transplanted organ, both acute and chronic, by about 15 to 60%, and can lead to possible graft loss.[13] In contrast, when the patient adheres positively to the proposed pharmacological treatment, it is possible to potentially avoid the unfavorable outcomes that can occur after transplantation, and it is of fundamental importance to understand the variables involved with drug adherence for optimal clinical intervention.[14]

There is the possibility of reducing the complexity of treatment for underlying diseases by selecting drugs with fixed combinations, as, for example, occurs between antihypertensive drugs and also insulins. It is also possible to avoid the use of two tablets to reach the dose of the drug, as in the case of levothyroxine or atenolol, when it is presented in the desired concentration. However, it should be noted that this reduction in complexity can sometimes compromise access to medicines, since the more complex prescription may have been made to ensure access to standardized drugs in the basic pharmaceutical care component and also via the *Aqui Tem Farmácia Popular* program.

It is worth discussing that in patients taking other drugs besides immunosuppressants, especially in those with more complex pharmacotherapy, the phenomenon of selective adherence can be observed, that is, patients adhere correctly to the immunosuppressant treatment and not to the rest of the treatment.[15,16] This situation deserves attention from the healthcare team, because the lack of control of diseases such as hypertension and diabetes can also reduce graft survival.

This study has limitations. The first is that the complexity classification adopted here was stipulated by means of the quartiles obtained for the group of patients seen at the outpatient clinic of the center studied, and there may be divergence for other sites due to the characteristics of the population studied and the protocols adopted. On the other hand, the profile of medication use was described for a sample of cases, and this may make transposition to other patient groups difficult. However, this study is the first to address this description of complexity for transplant patients in Brazil and demonstrates that immunosuppression, even if it makes the patient more susceptible to other health conditions and deserves special attention when adhering to medication, is not what makes the treatments complex, and this should be clearly understood by the entire health care team.

CONCLUSION

Patients with a higher number of drug doses and a more insulin-dependent condition associated with immunosuppressive pharmacotherapy are the most complex and, therefore, demand a greater need for follow-up because of the difficulties faced in adhering to treatment. In this sense, the health team must carry out an adequate scheduling, in addition to the orientation for the correct use of the medications, so that the greatest effectiveness and safety of the treatments are guaranteed.

AUTHORS' CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Soares LSS and Galato D; **Conception and design:** Soares LSS and Galato D; **Data collection, analysis and interpretation:** Simões IG, Soares LSS and Galato D; **Article writing:** Simões IG, Soares LSS and Galato D; **Critical review:** Simões IG, Soares LSS and Galato D; **Final approval:** Simões IG, Soares LSS and Galato D.

AVAILABILITY OF RESEARCH DATA

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