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Original Article

Medication Regimen Complexity Index After Kidney Transplant in Fortaleza, Brazil

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ABSTRACT

Background: The Medication Regimen Complexity Index (MRCI) is a reliable tool to evaluate the complexity of pharmacotherapy and can predict the treatment adherence of post-transplant patients. The MRCI was evaluated in the post-kidney transplant period. **Materials and Methods:** In a descriptive, observational, and cross-sectional study, we evaluated the pharmacotherapy and the MRCI of kidney transplant patients for a year in a kidney transplant outpatient clinic at a university hospital in Fortaleza, Brazil. A convenience sample was obtained and analyzed the records of kidney transplant recipients who had at least two visits with pharmacists. The main outcome measures are characterization of immunosuppressive regimen, MRCI score, correlations between MRCI score and a period post-transplant. **Results:** 109 patients were included in the study. The predominant class was antineoplastic and immunomodulating agents (27.7%), and the most frequent immunosuppressive regimen was tacrolimus, mycophenolate sodium and prednisone (63.30%). The mean points in MRCI were 46; minimum of 19 points associated with 3 drugs and maximum of 83.5 points with 16. About sections A, B and C of the MRCI, the means found were 2.60, 13.2 and 30.6 points, respectively. Correlations between MRCI score and number of medications were checked, and a period less than 180 days after transplantation had score >40 points. **Conclusion:** MRCI in the kidney transplant patient is linked to the number of medications, dose and additional instructions. To improve adherence to the treatment, patient orientation is necessary especially in the first year after transplant.

Keywords: Drug Therapy, Kidney Transplantation, Medication Adherence, Pharmaceutical Services.

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INTRODUCTION

Assessing the complexity of the therapy and its relationship to the clinical outcomes is crucial for identifying problems, optimizing the treatment and to promote treatment adherence of the patient.[1] In general, complex pharmacotherapies are determined by multiple characteristics of the prescribed regimen, including the number of medications in the regimen, number of doses per day and the interactions of the drugs with food intake.[2]

George *et al.* proposed an instrument to evaluate the pharmacotherapy complexity, which is called the "Medication Regimen Complexity Index" (MRCI). The instrument was later translated into Portuguese and validated for use in Brazil.[2,3] The use of validate MRCI measurements is important to compare similar studies performed in similar populations. In the MRCI, the dosing frequencies, nature of dosage forms, and the instructions that guide administration are the key factors contributing to complexity.[2]

In the last few decades, therapeutic regimens post-transplant has become more complex.[4] To improve patient´s adherence to drug therapy in this population, it is important to obtain knowledge of the immunosuppressive regimen, monitoring of serum drug concentrations and understanding of the patient's perception of the drug.[5] Studies show that the regime complexity may interfere with treatment adherence of the transplanted patient.[6,7]

In post-transplant, immunosuppressive therapy is essential since it prevents organ rejection and, consequently, graft loss. Usually,

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there is a combination of some drugs, including corticosteroids, calcineurin inhibitors, antimetabolites and mTor inhibitors. The combination of immunosuppressive agents is necessary because of their different mechanisms of action that lead to synergistic effects and decreased toxicity related to high doses.[8,9] However, the need for immunosuppression makes the recipient susceptible to infections that cause increased morbidity and mortality after transplantation.[10,11] Moreover, several drugs for the treatment of chronic diseases, such as hypertension and diabetes, and prophylactic drugs are used by patients in post-transplant, including antivirals, antibiotics, antifungals and anthelminthics, which lead to increasingly complex regimens.[12,13]

Among the professionals involved in the multidisciplinary team, the clinical pharmacist works by preventing, detecting, and solving problems and negative outcomes related to the therapy, both during hospitalization and hospital discharge.[14] The pharmacist plays an important role in reducing the regimen complexity and promoting adherence to pharmacological treatment, mainly through pharmacotherapeutic follow-up.[15-17] The pharmacotherapeutic follow-up is the service by which the pharmacist analyzes health conditions and risk factors of the patient to manage pharmacotherapy. The main objective is to prevent and to solve pharmacotherapy problems, achieving good clinical outcomes, reducing risks, and contributing to improved efficiency and quality of health care.[18]

The characterization of the medication regimen complexity index has been performed for different groups of patients, including subjects with diabetes,[19] psychiatric disorders,[20] coronary diseases,[21] HIV infection[22] and elderly.[23] However, studies involving transplant patients are scarce,[24] especially in Brazil. In that regard, the objective of the present study was to assess the complexity of pharmacological treatment regimens established in a population of kidney transplant patients attended in a clinical pharmacy service in Brazil.

MATERIALS AND METHODS

Setting

The study was performed in a clinical pharmacy service at the kidney transplant clinic of a university hospital in Fortaleza, Brazil, from January to December 2013. The study scenario consisted of a kidney transplant outpatient clinic from a public university hospital that provides health assistance of high complexity and is maintained by the Unified Health System (*Sistema Único de Saúde* - SUS) from Brazil. The Kidney Transplant outpatient clinic works from Monday to Friday from 7 A.M. to 7 P.M. with a multidisciplinary team (physicians, pharmacists, nurses, physiotherapists, psychologists, social workers, and nutritionists). This team offers a clinical monitoring service for both pre and post kidney transplant patients. The clinical pharmacy service was developed in 2011 and targets all the patients. The outpatient clinic has a private air-conditioned office for pharmaceutical care, which also include the patient´s families. Pharmacists perform a variety of services, ranging from review of the pharmacotherapy, drug therapeutic monitoring, elaboration of personalized instruments to facilitate adherence and guidance for the acquisition of drugs.

Study design and data collection

This was a descriptive, observational, and cross-sectional study. The pharmacotherapy of adult kidney transplanted patients was evaluated. A convenience sample was obtained and included data of kidney transplant recipients who had at least two visits with the pharmacists of the multidisciplinary team during the evaluated period. Patients who had incomplete demographic and clinical data were excluded.

In the pharmacy service, recent transplanted patients (up to 3 months post-transplant) are followed up weekly by the pharmacist after a routine medical consultation. After 3 months, consultations with the pharmacist occur on demand from health professionals or patients. Thus, recent transplanted patients have a higher frequency of consultations with both physicians and pharmacists. This is important to avoid graft rejection and to detect early real or potential problems related to the pharmacotherapy and adherence, and therefore there is no direct association between the number of consultations and the occurrence of problems associated with the drugs in use.

Data was collected from their medical records during the pharmaceutical consultation by the clinical pharmacist and included gender, age, transplantation cause, post-transplant time, level of education, prescribed drugs and their pharmaceutical forms, type of immunosuppressive regimen and dose frequency. Patient who was not seen by a pharmacist were not included in the study because the pharmacist, when detecting problems in the pharmacotherapy can recommend adjustments to regimen therapy that modify the complexity of therapy. All patients with at least two visits were included in the study, regardless of time after transplantation.

Pharmacotherapy was analyzed by using the medication regimen complexity index (MRCI) translated into Portuguese and validated for use in Brazil by Melchiors, Correr, Fernandez-Llimos (2007).[3] The MRCI consists of 65 items, divided into three sections, A, B and C, which include: (a) information on dosage forms; (b) frequency of doses; (c) additional instructions – such as specific times, drug use with food if necessary and dissolution in water. The total score of the MRCI is the sum of the scores of the three sections attributed to each drug.[3] The medications were recorded and classified according to the Anatomical Therapeutic Chemical (ATC) first level classification.[25] As this was a tool filled out by the health professional rather than the patient, its format allowed the records of multiple medications and additional information in the assessment, making it broader.

According to the protocol of the institution, the immunosuppressive drugs generally used in the post-transplant stage are prednisone, mycophenolate mofetil or sodium, tacrolimus, everolimus, sirolimus and cyclosporine. The choice of scheme depends on the characteristics of the patient and the donor and often corresponds to a triple immunosuppressive regimen, aiming to use low doses of each drug and reduce the occurrence of adverse reactions. Common post-transplant prophylactic drugs include omeprazole, nystatin, secnidazole, albendazole and ivermectin, sulfametozaxol / trimethoprim and isoniazid.

Table 1: Socio-demographic and clinical profile of renal transplant patients seen at the pharmaceutical service of renal transplant outpatient clinic of a university hospital in Fortaleza.

Variables		N (%)
Sex	**Male**	**53 (48.62)**
	Female	**56 (51.37)**
Underlying disease	Single right kidney + renal lithiasis	1 (0.92)
	Familial nephropathy	2 (1.83)
	Lupus	3 (2.75)
	Recurrent urinary tract infection (UTI)	3 (2.75)
	Diabetes mellitus (DM)	8 (7.34)
	Polycystic kidneys	9 (8.26)
	Arterial systemic hypertension	12 (11.00)
	Glomerulonephritis (GN)	32 (29.36)
	Undetermined	39 (35.78)
Age ranges: 14-77 Mean: 44.90 ±10.8, years	≤ 20 years	6 (5.50)
	21 – 40 years	34 (31.19)
	41 – 60 years	57 (52.29)
	> 60 years	12 (11.01)
Education levels	Not determined	28 (25.69)
	Incomplete primary education	22 (20.18)
	Complete primary education	22 (20.18)
	Complete secondary education	15 (13.76)
	Complete higher education	8 (7.34)
	Illiterate	9 (8.26)
	Incomplete secondary education	4 (3.67)
	Incomplete higher education	1 (0.92)
Total		109 (100.00)

Data and statistical analysis

The results were analyzed after processing the data with Statistical Package for Social Sciences (SPSS) software, version 20.0. After assessment of the variables, the data were analyzed in a descriptive manner and presented with tables and/or graphs. Numerical variables were described in the form of means and standard deviations, and categorical variables in the form of proportions. We used the chi-square test to see if the frequency at which a given event observed in a sample deviated significantly or not from what was expected and the *t*-test to compare the sample at the first and last visit for (the categorical and numerical variables), respectively, with significance set at $p<0.05$.

Ethics approval

Regarding the ethical aspects, the study was designed according to the regulations and guidelines for research involving human beings and approved by the Research Ethics Committee of the Federal University of Ceará (Number 05925513.2.1001.5054); this was part of the Pharmaceutical Care for Health Care Networks project in Ceará.

RESULTS

237 kidney transplant patients were seen and followed-up by pharmacists of the multidisciplinary team, but 109 met the inclusion criteria of pharmacotherapeutic follow-ups for the study (45.99%, n = 109/237). The remaining patients had only one pharmaceutical appointment during the study period and were therefore not included.

Most of the patients were male (51.37%, n = 56/109), and the most common age group was 41-60 years, (52.29%; n=57/109). The mean age was 44.90 ± 10.8 years (range: 14-77 years). The most prominent causes that led patients to seek kidney transplantation were undetermined (not defined causes) (34.86%; n = 38/109) and glomerulonephritis (20.18%; n = 22/109). The education levels that were reported and recorded in the follow-up of the pharmacotherapy show that complete and incomplete elementary education were the most common levels, each representing 20.18% (n = 22/109) patients (Table 1). The mean number of visits per patient was 3.3 ± 1.7 (range: 2-10). The mean post-transplant time was 585 days ± 745.4 (range: 12 days to: 20 years).

The total number of medications prescribed in all followed-up patients was 791, with a mean of 8.5 ± 2.6 (range: 3-16) medications per patient. The ATC classification showed that the predominant class in the study period was "antineoplastic and immunomodulating agents" with a frequency of 27.7% (n=219/791), followed by the medication class "alimentary tract and metabolism" in 21.7% (n=172/791) (Table 2). Regarding the immunosuppressive regimens prescribed per patient, 63.30%

Table 2: ATC first level classification of the drugs used by renal transplanted patients seen at the pharmaceutical service of renal transplant outpatient clinic of a university hospital in Fortaleza, Brazil.

Anatomical Group of ATC Classification	ATC code	N (%)
Antineoplastic and immunomodulating agents	L	219 (27.69)
Alimentary tract and metabolism	A	172 (21.74)
Cardiovascular system	C	124 (15.68)
Antiinfectives for systemic use	J	116 (14.66)
Systemic hormonal preparation, excluding sex hormones and insulins	H	94 (11.88)
Blood and blood-forming organs	B	42 (5.31)
Nervous system	N	16 (2.02)
Genitourinary system and sex hormones	G	4 (0.50)
Musculoskeletal system	M	3 (0.38)
Various	V	1 (0.13)
Total		791 (100)

(*n*=69/109) of the regimens were composed of tacrolimus, mycophenolate sodium and prednisone, followed by tacrolimus and mycophenolate sodium with 11.93% (*n*=13/109).

The total points mean in the MRCI scoring was 46±13.7; a minimum number of 19 points was associated with the use of three medications and a maximum number of 83.5 points associated with 16 medications with daily administration. When evaluating the dosage forms of the pharmacotherapy (section A), the mean number of points was 2.60±2.0 points (Table 3). Capsule/tablet formulation was present in all drug treatments. Liquid formulations (16.5%; *n*=18/109) and injectable vials (27.5%; *n* = 30/109) were also prescribed.

For dose frequency (section B), the mean score was (13.2 ±3.9). The most prescribed doses were the administration once a day and every 12 hr, present in treatment of all the patients from the study (Table 3). Regarding additional instructions (section C), the mean score was 30.6±9.1 points. The main instructions on drug treatment were to administer the medications at specific times and to avoid drug-food interactions, which were provided for all patients. The follow-up visits also included the following instructions for patients: administration of the drugs in multiple units (83.5%, *n*=91/109) and administration of the drugs in alternate doses (49.5%, *n* = 54/109).

When evaluating the MRCI score and the number of medications administered daily for the patients, the following correlations were found between MRCI score and the number of medications: a) 19-30 points: 3–5 medicines; b) 31–40 points: 5–7 medicines; c) 41–50 points: 8–10 medicines; d) 51–60 points: 10–11 medicines; e) 61–70 points: 11–12 medicines; and f) >70 points: 13–16 medicines.

In the period of 15–30 days, the most frequent score range for MRCI was 51–60 points (28%; *n*=7/25; 10–11 medications), followed by the range 41–50 points (24%; *n*=6/25; 8–10 medications). In the period of 31–60 days, 55% of patients (*n*=11/20) had a score of 41–50 points. On the other hand, patients in the post-transplant period 6 months – 1 year mostly had 31–40 points (41.7%; *n*=5/12; 5–7 medications). In the period > 1-year post-transplant, the majority with 44.8% (*n*=13/29) had 19–30 points (3–5 medications). The difference in points obtained regarding post-transplant time was statistically significant, where the majority of the patients with up to 180 post-transplant days had more than 40 points, which demonstrated a greater regime complexity, with this score corresponding to daily administration of seven medications (p <0.05) (Table 4).

DISCUSSION

MRCI is an instrument capable of measuring the complexity of pharmacotherapy, independently of socio-economic, pharmacological, or clinical variables.[2] To our knowledge, this is the first study to evaluate the complexity of pharmacotherapy using MRCI in adult patients after kidney transplantation performed in Ceará, Brazil. This study reinforces the importance of identifying specific components of the therapeutic regimen that increase the complexity of pharmacotherapy and provides an estimate of the ease (or difficulty) of patient compliance.[26]

The study population showed male predominance and the most common age group was 41–60 years. In a study conducted by Moura *et al.*, the predominant range of patients undergoing dialysis treatment was 45–64 years. The male predominance was consistent with other studies, which indicated a higher prevalence of renal failure in males than females.[27-30]

Most of the sample showed the highest level of schooling to be elementary education. According to Uchmanowicz, age and education levels may be related to the degree of adherence to treatment.[31] Regarding the patients' state of origin, data from the Brazilian Transplant Association (2013) show that the state of Ceará has the highest number of organ donors in the Brazilian population, which contributes to the arrival of patients from other regions of Brazil to Ceará and explains the presence of patients from other states in the hospital under study.[32]

The predominant underlying disease for end-stage kidney failure in the population was indeterminate cause, i.e., end-stage renal failure of uncertain cause, followed by glomerulonephritis and systemic arterial hypertension. Knowledge about the underlying disease that led to renal failure and transplantation is essential for the care of patients by the multidisciplinary team because there are diseases that require more specific immunological monitoring

Table 3: Mean, maximum and minimum values of complexity index of pharmacotherapy and of its prescription sections of renal transplanted patients seen at the pharmaceutical service of renal transplant outpatient clinic of a university hospital in Fortaleza, Brazil.

Medication Regimen Complexity Index	First Visit			*p* *
	Mean Points (±SD)	Minimum	Maximum	0.02
Section A	2.60 (±2.0)	1	7	
Section B	13.20 (±3.9)	6	24	
Section C	30.60 (±9.1)	11	58	
Mean total score	46.00 (±13.7)	19	83.5	

* *t*-test.

Table 4: Post-transplant time versus MRCI score at the visit of renal transplant patients seen at the pharmaceutical service of renal transplant outpatient clinic of a university hospital in Fortaleza, Brazil.

Post-Transplant Time	MRCI							*p**
	15–30 N (%)	31–40 N (%)	41–50 N (%)	51–60 N (%)	61–70 N (%)	> 70 N (%)	Total N (%)	
15–30 days	2 (8.0)	3 (1.02)	6 (24.0)	7 (28.0)	4 (16.67)	3 (12.0)	25 (100)	<0.05
31–60 days	2 (10.0)	0	11 (55)	4 (20.0)	1 (5.0)	2 (1.0)	20 (100)	
61–180 days	2 (8.70)	6 (26.09)	5 (22.0)	9 (39.13)	1 (4.35)	0	23 (100)	
6 months–1 year	2 (16.67)	5 (41.67)	2 (16.67)	2 (16.67)	0	1 (8.33)	12 (100)	
>1 year	13 (44.83)	6 (20.69)	6 (20.69)	4 (13.79)	0	0 (0)	29 (100)	

and may require changes in the immunosuppressive regimen.[33] In a study by Moura *et al.*, the main underlying disease for kidney failure was also of indeterminate cause.[34] However, systemic arterial hypertension and glomerulonephritis are frequent reasons for transplantation, as found by Wang *et al.*, during the pharmacotherapeutic follow-up of kidney transplant patients.[35]

The immunosuppressive regimen was also evaluated, and the predominant combination was tacrolimus, mycophenolate sodium and prednisone, which is in accordance with the protocol of the kidney transplant service of the hospital studied. Except for transplantation between identical twins, every kidney transplant recipient needs to receive immunosuppressive drugs and a combination of drugs with different mechanisms of action must be used to prevent the transplanted graft from being rejected.[8,9] Increased use of combination therapy with two, three or more immunosuppressive agents with different pharmacokinetic profiles and potentially capable of influencing each other may contribute to high inter- and intra-individual variability in the dose-concentration effect.[36] The optimization of doses and therapeutic regimens according to the peculiarities of patients to balance adequate immunosuppression with reduction of rejections and adverse events caused by pharmacotherapy (e.g., infections, metabolic disorders, cancer) are challenging goals in the clinical management of the transplanted patient.[37]

The MRCI of the pharmacotherapy of the patients in our study showed a statistically significant difference in scores (p <0.05) between the first and last visit of the period. The average number of medications used by patient was high and, according to the instrument developed by Melchiors, Correr and Fernandez-Llimos, the number of drugs used by patient has a great influence on the regime complexity but cannot be used as a single factor of analysis.[3] Post-transplant polymedication is a common situation and studies measuring and confirming the high complexity of post-transplant drug treatment are limited. Moreover, the regime complexity is likely to increase due to pharmacotherapeutic regimens and frequent dose changes in the post-transplant period.[6]

The use of many drugs increases the risk of adverse reactions and drug interactions, which can lead to treatment withdrawal, further contributing to the non-compliance of the transplant recipient with drug therapy.[38,39] Adherence to treatment is an important factor for successful transplantation to avoid acute rejection and graft loss, so transplant patients need specific care with adequate instructions.[40]

When comparing our results with those of Melchiors, Correr and Fernandez-Llimos, who employed MRCI in diabetic patients, we found that the relation between score and number of medications was divergent.[3] The lowest score in the present study was 19 points, which corresponded to three medications; in the Brazilian validation study, three medications had a score of 11.5 points. In addition, diabetic patients used a maximum of 12 medications (45.5 points), while kidney transplant patients used a maximum of 16 medications (>70 points).

In the study by Linnebur *et al*. with older adults with depression, the minimum number equal to one drug was associated with two points, and the maximum number of 18 drugs was associated with 47 points.[41] The evaluation performed by Diniz with asthmatic patients found that one drug corresponded to 5.5 points and 6 medications to 29 points.[42] Thus, regime complexity can be understood as an association between number of medications, dosage form, dose and additional instructions for the treatment, and the method adopted in this study to determine the regime complexity did not designate a cut-off value for the characterization of patients with highly complex drug regimen.[2,3]

The total score mean obtained was higher than the value reported by Kamila *et al*. when evaluating MRCI of kidney and liver transplant patients attended at two transplantation centers in the United States (Chicago and Atlanta).[6] In this study, kidney transplant patients had a mean score of 17.9 ± 8.1. The studies performed by Acurcio *et al*., Martínez and Ferreira and Diniz showed a total average of 6.1, 19 and 15.9 points, respectively, demonstrating that the kidney transplant patients evaluated in this study had higher mean of total points.[42-44] Section C (additional instructions) made the greatest contribution to the total score but did not differ significantly between the first and last visit, since guidelines on drug administration at specific times and drug-food interactions are followed as routine in the pharmacotherapy of patients after kidney transplant to promote adherence to treatment.[42-44]

Section A (dosage forms) showed that capsules and tablets were the common dosage forms in pharmacotherapy, while some patients also used the injectable form, with the profile changing at the end. Section B (dose frequency) showed that the highest number of prescriptions was every 12 hr and once daily. In section C (additional instructions), the instructions "take as directed," "take at specific times" and "take with/without food" were prevalent throughout the assessed period. When evaluating the drug treatment, the physician should evaluate not only the number of medications administered daily, but also the number of daily doses, frequency and special instructions for use.[45] Libby *et al*. evaluated MRCI in chronic diseases (depression in the elderly, HIV, diabetes and hypertension) and showed that dose frequency was an important component of regime complexity, as well as the variety of dosage forms.[46] Although higher rates of drug prescription were observed during the first year after kidney transplant, and greater frequency of dose and dose alternation, the MRCI score was found to be statistically significant with stratification of time in the kidney transplant period ($p<0.05$).

Our study provides valuable information on the complexity of pharmacotherapy in post-transplant patients in Ceará. However, it has some limitations. First, these results cannot be generalized to outpatient services which do not include clinical pharmacist follow-up. In addition, this was an unicentric study that was intended solely to assess clinical and demographic data of patients followed by clinical pharmacists within a multidisciplinary team. We did not assess costs, outcomes or correlations between MRCI and graft rejection. This type of study can be especially useful in devising strategies for stimulating adherence to pharmacotherapy and reducing its complexity, especially in polypharmacy and multidiagnostic situations. Further research should explore these issues in other health-care centers.

CONCLUSION

We conclude that MRCI in the kidney transplant patient is not only related to the number of drugs used but also to the "dosage form" and "frequency of doses." "Additional instructions" are present throughout the post-transplant pharmacotherapy. Therefore, it is important that the moment of orientation of the patients about the established pharmacotherapy be focused on the special care that must be taken in administering the drugs, to minimize non-adherence to treatment, mainly for patients in the post-kidney transplant period of less than one year.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

Authors' Contributions

BCCM: Data acquisition; **BCCM:** Data and statistical analysis; **BCCM:** Manuscript preparation; **IHFC, PYMF, EFC:** Statistical analysis; **BCCM, PYMF, IHFC, EFC:** Manuscript review and editing; **PFCBCF, BCCM, PFCBCF, MMFF:** Concept, Design, Definition of intellectual content; **MMFF:** Approval of article.

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