

ADHERENCE TO DRUG TREATMENT IN CHILDREN AND ADOLESCENTS WITH CYSTIC FIBROSIS

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ABSTRACT

Introduction: To assess adherence to pharmacotherapy in pediatric patients with cystic fibrosis, associating it with socioeconomic, clinical, and nutritional variables. **Methods:** Cross-sectional study, including patients aged 0 to 18 with a diagnosis of cystic fibrosis. To assess adherence, the self-report questionnaire Brief Medication Questionnaire (BMQ) and medication withdrawals from the pharmacy over 12 months were used. The average medication possession rate (CMPR) was calculated for each patient and classified into two groups: high adherence (≥ 0.8) and moderate/low adherence (< 0.8). The Shwachman-Kulczycki (SK) and Bhalla scores, spirometry, and nutritional diagnosis were obtained. **Results:** Of the 85 patients, 37.6% adhered to treatment according to the BMQ, and 64% according to the CMPR. The general analysis showed an association between CMPR and clinical score ($p=0.013$), Bhalla score ($p=0.02$), and better nutritional diagnosis ($p=0.045$). Dividing the groups by age, in the 0-5 age group there was an association between the family's socioeconomic factor, the CMPR ($p=0.017$), and the BMQ (0.008). In the 6-18 age group, there was an association between the CMPR and the body mass index (BMI) Z-score ($p=0.025$) and SK ($p=0.017$). There was also an association between adherence to the BMQ and the belief barrier ($p=0.022$). There was also an association between the CMPR and the body mass index Z-score ($p=0.017$), and SK ($p=0.025$), and an association between adherence to the BMQ and the belief barrier ($p=0.022$). **Conclusion:** Adherence to drug treatment by self-reporting was lower than adherence by collecting the drugs from the pharmacy. The clinical score of SK, Bhalla, and the nutritional diagnosis were directly correlated with the CMPR. There was an influence of the socioeconomic factor in younger patients (< 6 years), and for older patients (≥ 6 years) there was an influence of their belief barriers.

Keywords: Cystic fibrosis; Pediatrics; Adherence to treatment; Malnutrition; Exacerbation.

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INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive genetic disease that occurs more frequently in Caucasians and is caused by mutations in the gene that codes for the *cystic fibrosis transmembrane conductance regulator* (CFTR) protein. This gene is located on the long arm of chromosome 7¹. There are currently more than 2,000 mutations in this gene, with F508del being the most common².

The CFTR protein is found in the apical membrane of epithelial cells and functions as a chloride channel. When this channel is not functioning properly, there is a reduction in chloride secretion and an increase in sodium absorption, altering the viscosity of the excreted fluids and causing organ obstruction. A fault in CFTR can affect various systems in the body, resulting in pulmonary, gastrointestinal, and sweat gland manifestations, among others. The most reported complications are bronchiectasis, chronic and recurrent respiratory infections, pancreatic insufficiency, intestinal obstruction, vitamin deficiency, and malnutrition³.

Among these complications, chronic lung disease affects many CF patients. Drug therapy commonly includes the administration of bronchodilators, inhaled mucolytic agents to facilitate expectoration, inhaled antibiotics to suppress colonizing organisms such as *Pseudomonas aeruginosa*, as well as inhaled corticosteroids, oral antibiotics, and other drugs according to the need and severity of the disease⁴.

In addition to lung disease, another recurring comorbidity in CF patients is pancreatic insufficiency caused by obstruction of the pancreatic ducts, which prevents the secretion of pancreatic enzymes. The treatment for this complication is enzyme replacement therapy, which is often used, as well as a diet rich in proteins, calories, and fats to optimize nutritional parameters. Moreover, supplementation with fat-soluble vitamins, such as vitamins A, D, E, and K, is essential for this patient profile. Another complication is hepatobiliary disease, which is managed with ursodeoxycholic acid⁴.

There is currently no cure for the disease, but several therapies have been developed in recent decades to alleviate the symptoms. In addition to those mentioned above, CFTR modulators can be used (e.g. ivacaftor, lumacaftor, tezacaftor, elexacaftor) and in some cases, lung transplantation is considered⁵.

Adherence to the treatment of chronic patients is fundamental from the initial phase which requires commitment from the caregiver to the subsequent phases to guarantee adequate treatment and help the patient reach adulthood with greater quality and life expectancy. A study carried out in the United States on pediatric patients with CF showed that high adherence to treatment reduces morbidity and mortality. It also reduces health costs by decreasing hospitalizations and the use of medication⁶.

Among the factors cited in the literature, which are related to problems with adherence to treatment in pediatric CF patients, other factors are the lack of access to medication, the complexity of the treatment, difficulty swallowing pills, social problems, the presence or absence of symptoms, shame in administering medication in public places, lack of understanding of the benefits of medication, adverse effects of pharmacotherapy and the beliefs of each family⁷⁻⁹.

Studies of adherence in CF have their limitations because there is still no validated questionnaire available to measure this variable specifically in patients with CF. Treatment adherence can be verified through direct methods (serum drug dosage) or indirect methods (questionnaire, dispensing of medication, electronic device, and/or patient diary). The indirect method based on patient self-reporting is more viable but may overestimate adherence, while the direct method does not always have a viable application¹⁰.

Given the above, there is a need for a greater understanding of adherence to drug treatment in this population, given the benefits and general clinical improvement. In this context, this study aims to assess adherence to pharmacotherapy in pediatric CF patients, associating it with socioeconomic, clinical, and nutritional variables.

METHODS

A cross-sectional study was carried out at a CF referral center in a hospital in southern Brazil. The study population consisted of pediatric patients diagnosed with CF between the ages of 0 and 18 who were being followed up at the children's pulmonology outpatient clinic. Patients who did not collect their medication from the pharmacy in the state of Rio Grande do Sul, Brazil, were excluded. Data was collected during annual check-ups, where patients were invited to take part in the study. Those responsible for the patients signed an informed consent form and patients over the age of 10 signed an assent form. Two questionnaires were used: one to assess adherence and the other to assess the family's socio-economic situation.

To assess adherence to medication treatment, a validated questionnaire translated into Portuguese was used, the Brief Medication Questionnaire (BMQ). The questionnaire was answered by the caregiver and/or patient over 10 years of age^{11,12}. Patients were classified as adherent or non-adherent to treatment. For socioeconomic classification, a questionnaire based on points from the Brazilian Association of Research Companies was used, dividing the patient's family into 6 groups (A, B, C1, C2, D, and E) according to average family income. Group A1 is the highest class (better quality of life and higher purchasing power) and group E indicates the lowest class, with lower purchasing power and poor quality of life. This classification criterion takes into account the family's assets, place of residence, and level of education¹³.

Another measure of adherence was the frequency of drug withdrawals from the pharmacy by consulting the Rio Grande do Sul state pharmacy system. The following medicines were consulted: ursodeoxycholic acid, alfadornase, pancreatic enzymes, multivitamins, inhaled colistimethate, and inhaled tobramycin. This system allows you to view the date and quantity of medication (number of capsules, tablets, ampoules, or vials) supplied to the patient each month. The record of drug withdrawal per patient was obtained from the last twelve months before the patient's inclusion in this study. The medication possession rate was calculated by dividing the number of days the drug was supplied during the observed period by the number of days in the same period. The medication possession rate was calculated for each drug and then the average of a composite medication possession rate (CMPR) was calculated for each patient. The CMPR refers to the average number of withdrawals from the pharmacy of all the medicines used by the patient and is categorized into high adherence (>0.80) to treatment and moderate/low adherence (<0.80)⁶.

As for nutritional parameters, the patient's anthropometric assessment was carried out routinely by the team's nutritionist. The weight was measured

on a Filizola® electronic scale, with a maximum load of 150 kg, where the measured weight varies by 100g. To measure height, a Sanny® anthropometer was used, graduated in centimeters and with the smallest division in millimeters. The data collected during the consultation was weight, height, body mass index (BMI), weight for age, height for age, and body mass index for age, using the Z-score and percentile as criteria according to the growth standards of the World Health Organization¹⁴. The patients were classified according to their nutritional diagnosis into three groups: malnutrition/nutritional risk, eutrophic, and risk of overweight/overweight.

The patient's clinical condition was assessed by the attending pulmonologist using the Shwachman-Kulczycki (SK) score. The SK score is divided into four domains (general activity, physical examination, nutrition, and radiological findings) which are scored between 5 and 25, according to the degree of impairment. The SK score goes up to 100 points, with higher scores being associated with better clinical conditions^{15,16}.

Some data was obtained by analyzing the patient's medical records. To assess lung function, the most up-to-date spirometry of each patient was checked, recording forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and FEV1/FVC ratio, as well as the Z-score of FEV1 and FEV1/FVC. Chest CT scans of patients over 6 years of age were used for the Bhalla score, assessed by a radiologist^{17,18}.

Regarding bacterial colonization, the patient's last sputum or oropharyngeal swab was checked. According to Lee's criteria, patients with more than two samples positive for *Pseudomonas aeruginosa* in 6 months were considered to be chronically colonized¹⁹. Furthermore, the last hospitalizations for respiratory exacerbations and whether the patient was taking oral antibiotics at the time of the consultation were verified.

All the data was compiled and organized in an Excel 2019 spreadsheet and then submitted and analyzed using the *Statistical Package for the Social Sciences*, version 20.0.

Quantitative variables were calculated using the mean and standard deviation or median and interquartile range. The qualitative variables were described by absolute and relative frequencies. Non-parametric data was analyzed using the Mann-Whitney U-test and the Kruskal-Wallis test. Qualitative data was analyzed using the chi-square test. Correlations between the adherence score and the continuous variables were analyzed using Pearson's linear correlation test or Spearman's correlation coefficient. A significance level of 5% was established. Kolmogorov-Smirnov and Shapiro-Wilk normality tests were performed, and the Lilliefors correction was used.

The study was approved by the Research Ethics Committee of the Hospital de Clínicas de Porto Alegre and by the Ethics Committee of the School of Public Health of Rio Grande do Sul. Approval number: 43446721.0.0000.5327.

RESULTS

A total of 85 patients were included in the study out of 120 patients seen by the pediatric CF center between October 2021 and October 2022.

Table 1 shows the clinical, nutritional, and socioeconomic characteristics of the study participants.

Table 1: Socioeconomic, clinical, and nutritional profile of children and adolescents with Cystic Fibrosis in a reference center in Southern Brazil, n = 85

Features	n (%)
Sex	
Female	47 (55.3)
Male	38 (44.7)
Age (in years)	
0 – 5	34 (40.0)
6 – 18	51 (60.0)
Race	
White	81 (95.3)
Black	4 (4.7)
Mutation	
F508del heterozygote	45 (52.9)
F508del homozygote	28 (32.9)
Other	12 (14.1)
Socioeconomic assessment	
A	7 (8.2)
B1	7 (8.2)
B2	24 (28.2)
C1	24 (28.2)
C2	14 (16.5)
D-E	9 (10.6)
Nutritional Diagnosis	
Malnutrition/Nutritional Risk	19 (22.4)
Eutrophic	56 (65.9)
Overweight/Risk of overweight	10 (11.8)
SK score	
Excellent	47 (55.3)
Good	22 (25.8)
Medium	15 (17.6)
Moderate	1 (1.2)
Severe	0

SK: Shwachman-Kulczycki.

Adherence to drug treatment using the BMQ instrument was low, with 37% (32/85) of patients classified as adherent. Concerning the withdrawal of medication from the pharmacy, 64% adherence was obtained, with 55 patients classified as having high adherence and 30 patients as having moderate/low adherence. Self-reported adherence using the BMQ was relatively lower than the adherence score based on taking medication from the pharmacy, and there was no agreement between the two methods of adherence.

The BMQ questionnaire found that 42% of patients (36/85) had some negative belief associated with the use of the drugs reported and all patients were included as having a recall barrier due to the multiple doses of the drugs. Access to medication was inadequate for 75% (64/85) of patients, with the

lack of multivitamins being the most frequent barrier to access. In addition, 15% (13/85) of patients reported having stopped some medication in the last 6 months without a doctor's recommendation.

As for clinical status, the patients were classified as: 55.3% (47/85) excellent, 25.8% (22/85) good, 17.6% (15/85) average, 1.2% (1/85) moderate and no one had a severe condition. The 32 patients who self-reported treatment adherence had a median clinical score of 90 (interquartile range 10), while the 53 patients who self-reported non-adherence had a median clinical score of 85 (interquartile range 25).

Figure 1 shows the clinical score of SK by points according to the classification of adherence to drug treatment, both by BMQ and by taking the drugs from the pharmacy.

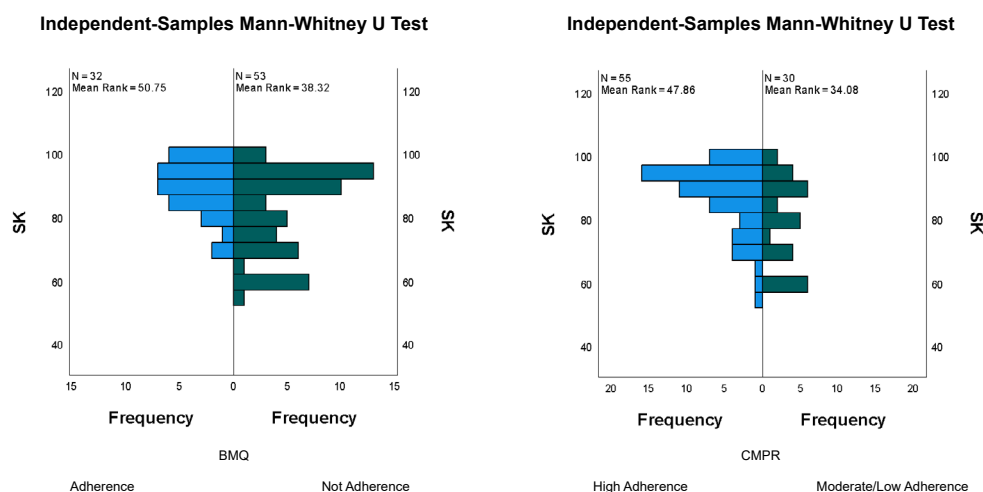


Figure 1: Adherence score (*Brief Medication Questionnaire* and *Compound Medication Possession Rate*, respectively) with the Shwachman-Kulczycki clinical score

The general statistical analysis showed a positive correlation between adherence to taking medication from the pharmacy with the SK clinical score ($r=0.306$, $p=0.013$), and a significant association between adherence to taking medication from the pharmacy with the Bhalla score ($r=0.206$, $p=0.02$) and with a better nutritional diagnosis ($p=0.045$). Regarding nutritional diagnosis, a difference could be observed between the nutritional groups when comparing adherence to drug withdrawals from the pharmacy: overweight/risk of overweight ($p=1.00$), eutrophic ($p=0.543$), malnutrition/nutritional risk ($p=0.039$).

It was not possible to observe an association between the variable of adherence to medication treatment and the presence of bacterial colonization (*Pseudomonas aeruginosa*, methicillin-sensitive *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus*, and *Burkholderia cepacia*), as well as the use of antibiotics at the time of consultation.

Due to the difference in the variables analyzed according to patient age, the patients were divided into two groups: 0-5 years ($n=34$) and 6-18 years ($n=51$). Regarding the group aged between zero and five (Table 2), an association was observed between adherence to treatment by withdrawing medication from the pharmacy and socioeconomic assessment ($p=0.017$) and between adherence to treatment by BMQ and socioeconomic assessment ($p=0.008$). The other variables analyzed using the two adhesion methods were not statistically significant.

In the analysis of the other group, aged between six and eighteen (Table 3 and Table 4), there was a significant association between adherence using the BMQ and the belief barrier ($p=0.022$) and a positive correlation between adherence using the withdrawal of medication from the pharmacy with the clinical SK score ($r=0.333$, $p=0.017$) and the BMI Z-score ($r=0.313$, $p=0.025$).

Table 2: Clinical and categorical variables of the 0-5 age group associated with withdrawing medication from the pharmacy and BMQ

	Medication from the pharmacy			BMQ		
	High adherence n=13	Moderate/ low adherence n=21	p	High adherence n=13	Moderate/ low adherence n=21	p
Age, years (median-II)	2 (2)	3 (3)	0.243	2 (2)	2 (3)	0.861
Age at diagnosis, days (median-II)	43 (61)	67 (46)	0.091	45 (50.5)	49 (69.5)	0.529
Weight for Age Z-score (median II)	0.19 (1.27)	-0.12 (2.22)	0.468	0.19 (1.3)	-0.12 (2.0)	0.972
Height for Age Z-score (median-II)	0.1 (1.28)	-0.98 (1.92)	0.258	0.32 (1.4)	-0.31 (1.9)	0.420
SK Clinical Score, points (median-II)	95 (15)	90 (15)	0.153	95 (12.5)	90 (15)	0.096
Sex (F/M)	9/14	5/6	0.726	5/8	9/12	0.800
Race (White/Black)	22/1	9/2	0.183	13/0	18/3	0.154
F508del heterozygote, n	15	8		9	14	
F508del homozygote, n	5	3	0.451	3	5	0.980
Other mutations, n	3	0		1	2	
Malnourished/Nutritional risk, n	3	4		2	5	
Eutrophic, n	19	5	0.086	11	13	.450
Overweight/Risk of overweight	1	2		0	3	
Belief Barrier, n (% cases)	9 (39.1)	3 (27.3)	0.498	3 (23.1)	9 (42.9)	0.241
Recall Barrier, n (% cases)	23 (100)	11 (100)	.a	13 (100)	21 (100)	.a
Access Barrier, n (% of cases)	18 (78.3)	9 (81.8)	0.810	11 (84.6)	16 (76.2)	0.555
Socioeconomic classification A-C1, n (% of cases)	18 (78.3)	4 (36.4)	0.017	12 (92.3)	10 (47.6)	0.008
Socioeconomic classification C2-E, n (% of cases)	5 (21.7)	7 (63.6)		1 (7.7)	11 (52.4)	

II: Interquartile range; SK: Shwachman-Kulczycki; a. All individuals were classified with this barrier.

Table 3: Association between the categorical variables of the 6-18 age group using the BMQ method

	High adherence n = 19	Moderate/low adherence n = 32	p
Sex (F/M)	10/9	14/18	0.539
Race (White/Black)	18/1	32/0	0.190
F508del heterozygote, n	9	13	0.589
F508del homozygote, n	8	12	
Other	2	7	
Malnourished/Nutritional risk, n	4	8	0.953
Eutrophic, n	12	20	
Overweight/Risk of overweight, n	3	4	
Belief Barrier, n (% cases)	5 (26.3)	19 (59.4)	0.022
Recall Barrier, n (% cases)	19 (100)	32 (100)	.a
Access Barrier, n (% of cases)	13 (68.4)	23 (71.9)	0.794
Economic classification A-C1, n (% of cases)	17 (89.5)	23 (71.9)	0.140
Economic classification C2-E, n (% of cases)	2 (10.5)	9 (28.1)	

a. All individuals were classified with this barrier.

Table 4: Correlation between adherence to treatment by withdrawing medication from the pharmacy and clinical variables in the 6-18 age group

	Correlation coefficient	p
Age (years)	-0.103	0.471
Age at diagnosis (days)	0.248	0.079
Height for Age Z-score	-0.076	0.594
BMI Z-score	0.313	0.025
SK clinical score	0.333	0.017
Bhalla radiological score	0.206	0.146
FEV1 Z-score	0.089	0.533
FEV1/FVC z-score	-0.026	0.855

BMI: Body Mass Index; SK: Shwachman-Kulczycki; FEV1: forced expiratory volume in the first second; and FVC: forced vital capacity .

DISCUSSION

As the findings in the literature show, this study also corroborates the hypothesis that adherence in individuals with CF is low^{7,20}. When analyzing the adherence instruments used, there was no agreement between the two methods BMQ and CMPR ($k=0.04$). The hypothesis is that self-reported adherence measures the patient's perception at the time, while

the medication possession rate assesses adherence over a given period.

Some barriers were identified in this study, which may explain the lack of adherence to treatment. Even though patients collect their medicines from the state pharmacy, the multivitamin presented a barrier in terms of access. The lack of this drug on the market is evident, and patients have to look for other alternatives

to make up for the lack of these fat-soluble vitamins. Many of them could not afford these expenses.

Another barrier observed was in relation to remembering to take the medication. All the patients obtained a positive score for barrier to recall due to the multiple-dose medication regimen (2 or more times a day), which makes it difficult to remember what they take. Most patients use pancreatic enzymes before each meal or diet, and depending on the instrument used, it is a barrier to remember to take the medication.

Some negative beliefs observed and reported by caregivers or patients throughout the study were related to a lack of knowledge about the efficacy of certain medications and concern about the long-term use of prescribed medications.

This study suggests that CF patients with poor adherence to drug treatment have a worse clinical state and are more malnourished or at nutritional risk. It is also suggested that patients under the age of 5 who are dependent on a caregiver to administer their medication may have low adherence if it is related to a low socioeconomic factor in the family. Patients over 6 years of age who do not adhere to treatment may be related to some negative family beliefs.

The self-reported adherence score was significantly lower than the score for withdrawing medication from the pharmacy, which suggests that the perception of the patient or guardian is that they are not adhering well to the treatment while they are in fact adhering well. Adherence using the BMQ method suggests adherence to treatment at the time, while adherence using drug withdrawal from the pharmacy suggests adherence over one year. Individuals who are adhering to treatment at the moment may not have adhered to it over the course of the year, and the same applies to those individuals who did not adhere to treatment well that week but made the effort to do so over the year.

The two adherence methods evaluated in this study showed a positive correlation between adherence and the patient's clinical status. Patients with better clinical status according to the SK score have better adherence to treatment with their medication. The study suggests that patients who tend to have better adherence seem to have a better clinical state

as well. Recently, CFTR modulators have been used in Brazil, and studies on treatment adherence have demonstrated excellent adherence due to clinical efficacy and ease of oral administration, maintaining significantly higher rates than traditional inhaled therapies. However, long-term follow-up reveals a statistically significant decline in adherence rates over three years, suggesting that initial motivation may be affected by chronic treatment fatigue²¹⁻²³.

Another finding was that patients in the malnourished or nutritional risk group seemed to have lower adherence than eutrophic patients and those classified in the obesity risk or obese group.

One of the limitations of this study was the difficulty in finding a suitable instrument to measure adherence to drug treatment. There are various direct and indirect methods for assessing adherence, but no gold standard and no specific instrument validated for this group of CF patients. In addition to the fact that the assessment of adherence in this study focused only on medication, CF is a complex disease that also includes adherence to diet, physiotherapy, and physical activity, which may have influenced the outcomes. Another possible limitation is self-report bias, which can overestimate or underestimate adherence, resulting in data that do not reflect reality.

In conclusion, the study shows that adherence varies according to the method used. Self-reported adherence to drug treatment in pediatric patients was low. However, greater adherence was observed when medication was taken from the pharmacy. The SK clinical score was directly correlated with both adherence methods, showing that better adherence contributes to a better clinical status. Dividing the groups by age, it was possible to observe the relationship between the family's low socioeconomic level and poorer adherence among children under 5. It was also observed that patients in the group aged 6-18 with low adherence to treatment were related to some negative beliefs, presenting a low BMI Z-score and a low SK score. Finally, some suggestions for practical strategies to improve adherence include the use of electronic reminders, follow-up by a clinical pharmacist, continuing education for caregivers, and multidisciplinary interventions.

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