Jornal de Assistência Farmacêutica e Farmacoeconomia
v.11, n.1, 2026.
Original Article

Treatment adherence in individuals with cystic fibrosis: An Observational Study

Adesão ao tratamento em indivíduos com fibrose cística: um estudo observacional

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How to cite:
Fontenelle FM, Vieira LS, Faiçal AB, Brazil JC, Teixeira MCA, D'Souza EL. Treatment adherence in individuals with cystic fibrosis: An Observational Study. JAFF [Internet]; 2026; 10(4); Doi: 10.22563/2525-7323.2026.v11.e00259

Received in: 07/31/2025

Accepted for publication on: 10/20/2025

ABSTRACT

Introduction: Low treatment adherence is a complex issue frequently observed in cystic fibrosis (CF) patients. **Objective**: To evaluate the self-reported treatment adherence rate and the rate determined based on pharmacy medication dispensation records in individuals with CF, and to investigate the association between treatment adherence and sociodemographic variables**. Methods:** Cross-sectional study with a consecutive sample was conducted in a CF referral center in the Northeast of Brazil. Using two methods: (1) The Morisky-Green test measured the self-reported treatment adherence for pancreatin, dornase alfa, and inhaled tobramycin; (2) dispensation records of prescribed drugs. A medication usage percentage ≥ 80% was classified as good treatment adherence. Prevalence ratios were used to assess associations between good treatment adherence and studied variables**. Results**: Forty-two individuals were included, 55.8% female, median age 7.3 years. Self-reported good treatment adherence for the use of pancreatin, dornase alfa, and inhaled tobramycin were 65.8%, 50.0%, and 44.4% of the participants, respectively. According to pharmacy records, the percentages of good treatment adherence were 71.4%, 66.7%, and 52.6% for the use of dornase alfa, tobramycin, and pancreatin, respectively. When comparing the methods, the agreement in treatment adherence rates for medication use ranged from 64.0% to 85.7%. **Conclusion**: Treatment adherence was low and varied by medication and methodology. Good adherence was mainly associated with younger age and the lower-level education of caregivers.
Keywords: Mucoviscidosis; children; teenagers; adherence; treatment.

RESUMO

Introdução: A baixa adesão ao tratamento é uma questão complexa frequentemente observada em pacientes com fibrose cística (FC). **Objetivo**: Avaliar a taxa de adesão ao tratamento autorrelatada e a taxa determinada com base nos registros de dispensação de medicamentos da farmácia em indivíduos com FC, e investigar a associação entre adesão ao tratamento e variáveis sociodemográficas. **Métodos**: Estudo transversal com amostra consecutiva, conduzido em um centro de referência para FC no Nordeste do Brasil, utilizando dois métodos: (1) O teste de Morisky-Green mediu à adesão ao tratamento autorrelatada para pancreatina, dornase alfa e tobramicina inalatória; (2) registros de dispensação de medicamentos prescritos. Uma porcentagem de uso de medicamentos ≥ 80% foi classificada como boa adesão ao tratamento. Razões de prevalência foram utilizadas para avaliar as associações entre boa adesão ao tratamento e as variáveis estudadas. **Resultados**: Quarenta e dois indivíduos foram incluídos, 55,8% do sexo feminino, com mediana de idade de 7,3 anos. A boa adesão ao tratamento autorrelatada para o uso de pancreatina, alfadornase e tobramicina inalatória foi de 65,8%, 50,0% e 44,4% dos participantes, respectivamente. De acordo com os registros da farmácia, os percentuais de boa adesão ao tratamento foram de 71,4%, 66,7% e 52,6% para o uso de alfadornase, tobramicina e pancreatina, respectivamente. Ao comparar os métodos, a concordância nas taxas de adesão ao tratamento para o uso de medicamentos variou de 64,0% a 85,7%. **Conclusão**: A adesão ao tratamento foi baixa e variou de acordo com o medicamento e a metodologia. A boa adesão esteve associada principalmente à idade mais jovem e ao menor nível de escolaridade do cuidador.
Palavras-Chave: Mucoviscidose; crianças; adolescentes; adesão; tratamento.

Introduction

Cystic fibrosis (CF) is a hereditary, autosomal recessive, progressive, and potentially lethal disease. It is caused by pathogenic variants in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.[1,2] This gene encodes the CFTR protein, and the absence or defect of this protein causes an electrolyte imbalance, which underlies the disease pathophysiology. More than 2,000 variants have been identified in the CFTR gene, with the pathogenic F508del variant being the most common worldwide in CF, including in Brazil.[3,4]

CF is a multisystemic, chronic, highly pleomorphic disease. It exhibits a wide diversity in genotypic and phenotypic expressions presenting variable clinical symptoms and severity either from at birth or throughout life.[5-7] Typically, it is characterized by progressive lung disease, exocrine pancreatic dysfunction, along with elevated concentrations of chloride and sodium in sweat.[8-11]

Due to its chronic and progressive nature, CF requires complex and continuous treatment, with symptomatic medications that need to be administered multiple times a day to improve quality of life.[7,12] Depending on the severity of the disease, daily treatment can last from 2 to 4 hours and may include a large number and variety of oral, inhaled, subcutaneous, or intravenous medications.[13] The quantity and dosage of medications for individuals with CF differ according to age and stage of the disease.[14] Additionally, daily respiratory physiotherapy sessions, airway clearance, regular physical activity, and device cleaning are crucial. It is also important to maintain a well-nourished state, which may require pancreatic enzymes and nutritional supplementation, as well as a continuous specific diet.[15,1]

The treatment adherence (TA) is an essential and indispensable aspect for people with CF, as it contributes to increasing survival and improving prognosis of disease.[11,16] According to the World Health Organization (WHO), adherence is "the extent to which a person's behaviour — taking medication, following a diet, and/or executing lifestyle changes — corresponds with agreed recommendations from a health care provider". TA is an indispensable link between the prescriptions and the therapeutic result; therefore, adherence is a determining factor in treatment, as it allows the transmitted guidelines to be really followed and, consequently, a satisfactory response to be achieved, that is, the improvement of clinical status and quality of life.[17,18]

The considerable amount of time that is spent daily in administering prescription medicine constitute considerable challenges, creating significant barriers to adherence and making it difficult to maintain regular pharmacological treatment.[9,19] Low TA is a major public health problem, which is a challenge for individuals with CF and their families, impairing the performance and effectiveness of treatment, causing damage to the quality of life and increasing health expenses.[19,20]

There is a scarcity of studies on TA in people with CF (PwCF) in Brazil. Identifying the level of TA in this population can contribute to improving it, which is important not only for PwCF and their families but also for both public and private health systems, providing support for the planning of patient-centered care strategies, promoting the rational use of medicines, and contributing to cost reduction and improvement in the quality of life of PwCF. Therefore, the present study aimed to evaluate the self-reported TA rate, and the rate determined based on pharmacy medication dispensation records in PwCF receiving care in a Brazilian referral center and to investigate the association between treatment adherence and sociodemographic variables.

Methods

A cross-sectional study was conducted between February 2020 and February 2021 in an interdisciplinary CF outpatient department (AIFC) at a teaching hospital in the Northeast of Brazil. This referral center predominantly provides care to children and adolescents through weekly interdisciplinary consultations. Approximately 60 from different cities within the state, including the capital receive assistance. Individuals typically have quarterly consultations, which are more frequent for those under two years of age or when necessary for other age groups.

The sample selection was consecutive, and patients with CF diagnosed by two positive sweat tests (Chloride ≥60 mEq/L) and/or identification of two pathological *CFTR* gene variants, who regularly

used at least one CF medication dispensed at the Referral Center and followed up for at least three months, were invited to the study. Participants who responded incompletely to the questionnaires used in the study were excluded.

Data collection was performed prospectively during a consultation, at which time participants were asked to complete the "*Adherence to CF Treatment*" form. The instrument contained, but was not limited to, the 4-item Morisky-Green-Levine Medication Adherence Scale (MGLS). MGLS contains four issues referring to the use of each prescribed medication, and one affirmative answer to any of these questions classifies the individual as non-adherent to treatment.[21,22]

Sociodemographic characteristics, data on pharmacological treatment and the registration of variables possibly associated with compliance, as well as data on caregivers, were also collected using this instrument "*Adherence to CF Treatment*." Clinical variables related to the frequency of use of antibiotics administered either intravenously or orally, due to pulmonary exacerbations, were also recorded on this form.

Participants of 14 years of age or more answered the questionnaire themselves, while parents/guardians completed the form for those under 14 years old. Data regarding drugs prescribed, the amount dispensed and used, and the date of dispensing and of the patient returning to the pharmacy were registered on a dispensing form, based on which the amount of the drugs used was calculated.

The obtained data were registered in a standard form, stored in Microsoft Excel® version 365 program and processed in R 4.0.4 program. Since the study did not use a probabilistic sample, statistical inference was not used. The descriptive analysis consisted of calculating simple and relative frequencies of the studied variables. Continuous variables with normal distribution were described as mean and standard deviation (SD) and non-normal ones as median and interquartile range (IQR). The MGLS was used to assess self-reported adherence to pancreatic enzyme supplementation, dornase alfa and continuous inhaled tobramycin. The adherence rate for each pharmacy dispensed drug was analyzed considering the dispensed amount, according to the medical prescription and the return period. When the percentage of use of the dispensed drugs was ≥ 80%, compliance was considered good, as previously defined by Leite and Vasconcellos.[23]

Prevalence ratios (PR) were calculated to evaluate the association between compliance and sociodemographic. Agreement between the percentages of TA measured through each used instrument and for each medication prescribed was recorded.

This study is part of a project entitled: "*Evaluation of adherence to treatment for cystic fibrosis in children and adolescents in a multidisciplinary care center*". The Institute's internal review board approved that study protocol under approval letter 843.869 of October 23 and free and informed consent form was obtained.

Results

A total of 43 CF patients were included. The median (interquartile range [IQR]) age was 7.3 years [3.4- 12.4]. Median age (IQR 0.7 - 11.2) at CF diagnosis was 1.5 years. Twenty-four participants (55.8%) were female, 14 individuals (32,6%) lived together with up to 3 persons and 29 (67.4%) individuals lived at home with 4 or more people.

In total, 22 participants (51.2%) had a monthly family income of ≤1 minimum wage, with a median per capita income of R$348.00 (IQR 261.00 - 870.00) and 27 (62.8%) families were beneficiaries of a government financial support program (continuous cash benefit). A total of 39 participants (90.7%) had caregivers who usually administered their medications. The Table 1 sociodemographic characteristics of the studied population.

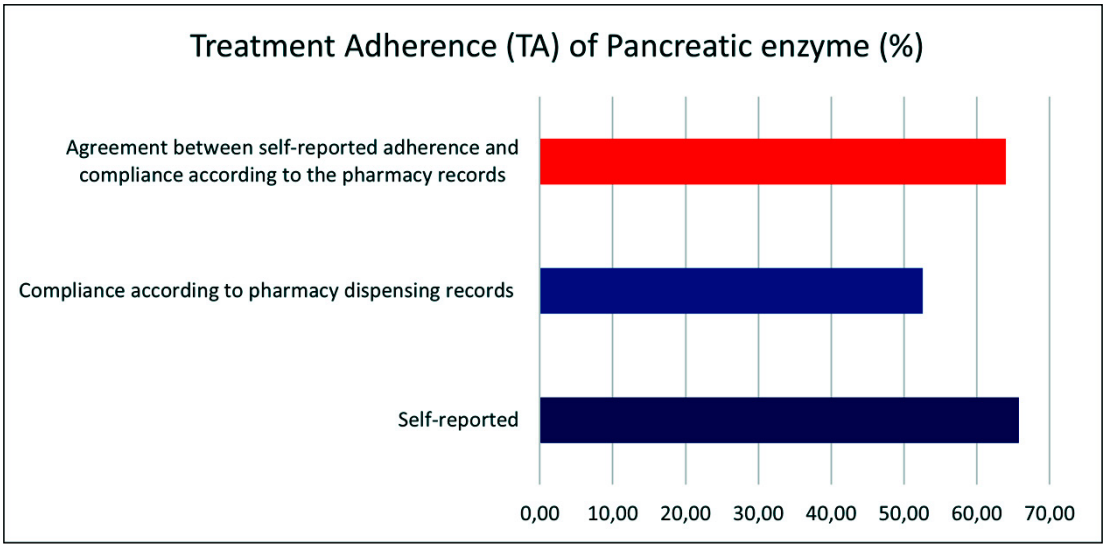
A total of 15 participants (34.9%) using ≤2 different drugs, and 28 (65.1%) routinely using >2 drugs were recorded. Overall, 38 individuals (88.4%) used pancreatic enzyme supplementation, 28 (65.1%) used inhaled dornase alfa and 9 (20.9%) were in continuous use of inhaled tobramycin. In the self-report, the rate of good adherence to pancreatin (65.8%) was higher compared to use of inhaled medications. Whereas the rate of good adherence to inhaled dornase alfa was higher according to pharmacy dispensing records (71.4%). The figure 1 shows data regarding medicine use and TA rates.

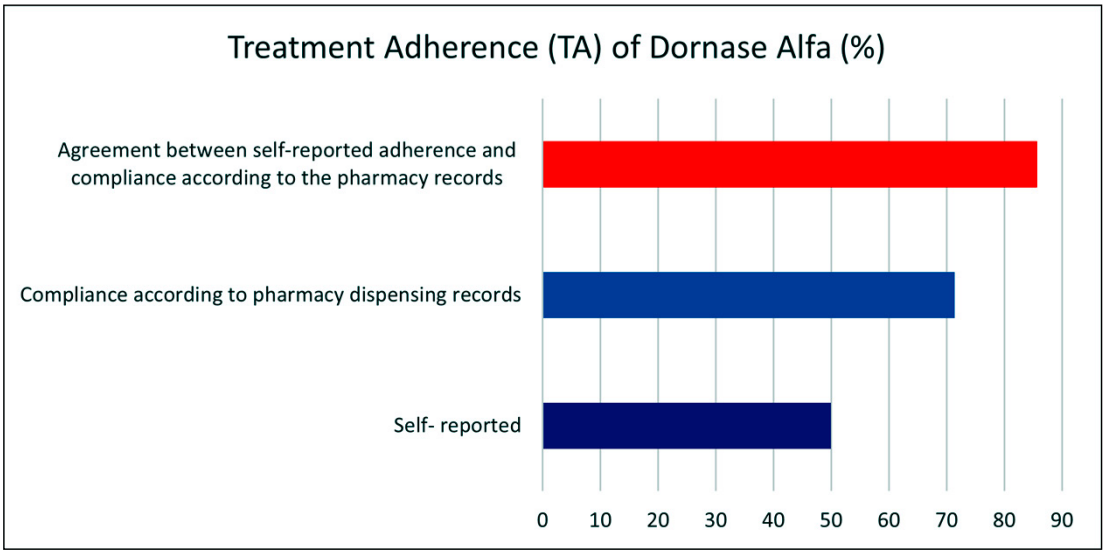
Table 1. Sociodemographic characteristics of the studied population, 2020-2021.

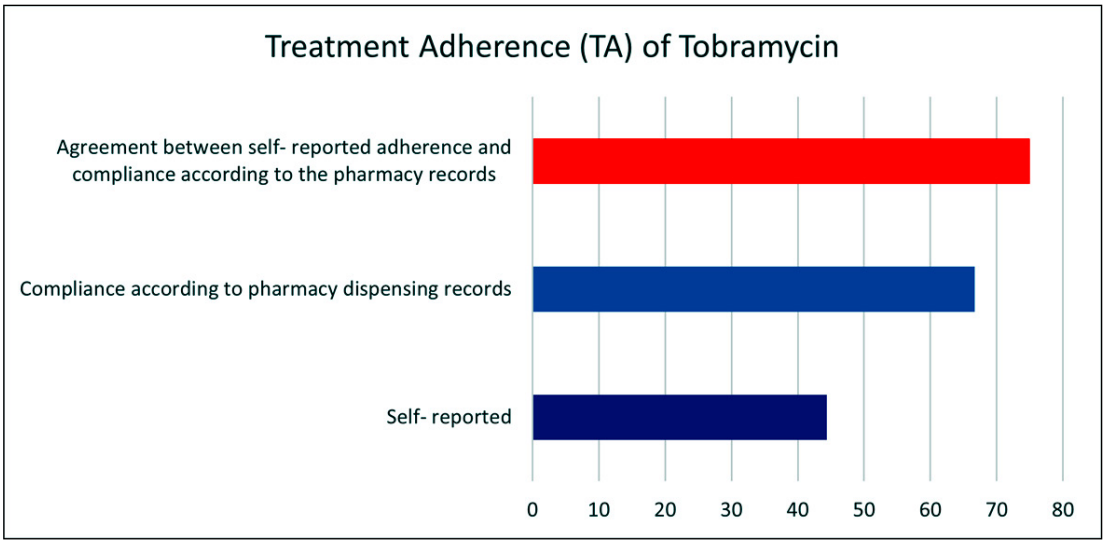
Variables	N total = 43
Median (Q1-Q3) current age (years)	7.3 (3.4 – 12.4)
Current age, n (%)	
< 14 years	34 (79.1)
≥ 14 years	9 (20.9)
Median (Q1-Q3) age at diagnosis (years)	1.5 (0.7 – 11.2)
Age at diagnosis n (%)	
< 1 year	25 (58.1)
≥ 1 year	18 (41.9)
Sex, n (%)	
Masculine	19 (44.2)
Feminine	24 (55.8)
Number of people residing in the household, n (%)	
Up to 03 people	14 (32.6)
04 or more people	29 (67.4)
Monthly Family income, R$ Median (Q1-Q3)	1045 (1045 - 3125)
Monthly Family income category, n (%)	
Up to 01 Minimum Wage	22 (51.2)
> 01 Minimum Wage	21 (48.8)
Renda per capita mensal, R$ Median (Q1-Q3)	348.3 (261.2 - 870.6)
Receiving some type of social benefit, n (%)	
Yes	27 (62.8)
No	16 (37.2)
Responsible, for administering medications n (%)	
Patient Caregiver	4(9.3) 39(90.7)
Education of the person responsible for administering medications, n (%)	
Incomplete elementary education	12 (27.9)
Complete primary education	1 (2.3)
Incomplete high school	4 (9.3)
Complete high school	18 (41.9)
Incomplete higher education	0 (0)
Complete higher education	8 (18.6)

Source: Research data, 2021

Figure 1. Drugs used, self-reported adherence to treatment and adherence according to the pharmacy dispensing records for 43 individuals with cystic fibrosis







There was higher association between self-reported TA to the use of pancreatic enzyme supplementation and patients <14 years old (PR=2.15), poor education of those who administered the medication (PR=1.63), beneficiaries of continuous cash benefit (PR=1.46) and female (PR=1.35). Higher self- reported adherence rates with the use of dornase alfa were associated with poor education for the person who is responsible for administering the medicine (PR=1.54), age of the patient <14 years (PR=1.46) and female (PR=1.16) (Tables 2 and 3).

Discussion

In this study, adherence rates were low for both methods assessed. The results showed varying percentages of TA depending on the drug and the evaluation method. Self-reported TA was higher for pancreatic enzyme supplementation (65.8%) compared to inhaled medications. This is likely due to the short-term perceived benefits of pancreatic enzymes, such as improved digestion and weight gain. In contrast, the benefits of inhaled medications are not immediately perceived.[24] Adherence to dornase alfa was higher (71.4%) when measured through pharmacy dispensing records. Higher self-reported TA rates were associated with younger age, lower education level of the caregiver, and receipt of continuous support benefit.

Despite the greater complexity of the use of medication, higher TA rates were observed for inhaled drugs, which were calculated through pharmacy records, whereas TA for dornase alfa was superior to continuous use of tobramycin, and it is probably due to dosage for each drug. There was also a greater TA concurrence for dornase alfa between the two methods in this study. The use of dornase alfa in comparison with pancreatic enzymes is a simpler dosage. Pancreatic enzymes have big variations in dosage and many particularities in use, varying according to the type, frequency and amount of ingested food, as the individual's food plan.[25] Thus, pancreatic enzymes showed less TA concurrence rates, for both methods. It is probably due to differences in the regimen of these drugs;[10] so only one dose/day of dornase alfa is required while pancreatic enzyme supplementation is administered at each meal.

Table 2. Assessment between self-reported therapeutic adherence to pancreatic enzymes and sociodemographic and clinical variables in individuals with cystic fibrosis from a Reference Center in Northeast Brazil. Interdisciplinary Cystic Fibrosis Outpatient Clinic, Salvador, 2020-2021.

Variables	Self-reported adherence		
	Adherent (n=25)	Non-adherent (n=13)	PR
Current age, n (%)			
< 14 years	23 (71.9)	9 (28.1)	2.15
≥ 14 years	2 (33.3)	4 (66.7)	1
Sex, n (%)			
Female	15 (75)	5 (25)	1.35
Male	10 (55.6)	8 (44.4)	1
Receives some type of social benefit, n (%)			
Yes	19 (73.1)	7 (26.9)	1.46
No	6 (50.0)	6 (50.0)	1
Education of the person administering the medication, n (%)			
Up to complete elementary school	10 (90,9)	1 (9,1)	1,63
Incomplete high school to complete higher education	15 (55,6)	12 (44,4)	1

Source: Research data, 2021.

Table 3. Assessment between self-reported therapeutic adherence to dornase alfa and sociodemographic and clinical variables in individuals with cystic fibrosis from a reference center in Northeast Brazil. Interdisciplinary Cystic Fibrosis Outpatient Clinic, Salvador, 2020-2021.

Variables	Self-reported adherence		
	Adherent (n=14)	Non-adherent (n=14)	PR
Current age, n (%)			
< 14 years	11 (55)	9 (45)	1.46
≥ 14 years	3 (37.5)	5 (62.5)	1
Sex, n (%)			
Female	9 (52.9)	8 (47.1)	1.16
Male	5 (45.5)	6 (54.5)	1
Education level of the person administering the medication, n (%)			
Up to complete elementary school	7 (63.6)	4 (36.4)	1.54
Incomplete high school to complete higher education	7 (41.2)	10 (58.8)	1

Source: Research data, 2021

This center provides pediatric care and 80% of patients are under 14 years of age. The younger group showed best results for adherence to medicines. Presence of family members in treatment is very common in this population, as drugs are usually administered by family caregivers, which may explain best adherence rates in this age group. This finding corroborates the study conducted by Zindani *et al*.,[26] who evaluated the effect of the child's age and parental supervision on adherence, and showed the importance of family participation in improving adherence to treatment in American children and adolescents with CF. Nevertheless, in the present study, even among youngest people, adherence rates were low.

As was found in several studies, TA decreases considerably in adolescence. This is a transition period, being a challenging phase for individuals and their families, when they will assume responsibilities, which often results in a decrease of TA, which can lead to a decrease in lung function and comorbidities that are associated with CF.[27] It is a crucial moment to reinforce therapeutic education, in order to increase TA in adulthood.[9] Thus, it is necessary to prepare children with CF for the arrival of puberty, teach them the characteristics of their disease, focusing on the importance of treatment, involving them in aspects of their daily care and gradually making them responsible for managing their own treatment, thus creating strategies to improve adherence throughout life.[20,26]

Sociodemographic characteristics impacted adherence to treatment in the present study. Surprisingly, caregivers with lower education levels, specifically up to elementary school, who received continuous cash benefit for chronic diseases showed better adherence rates to the analyzed drugs. This may be due to the free distribution of the medications by the Unified Health System (SUS) and the fact that most of the caregivers do not have a paid employment, allowing them more time to focus on the treatment of individuals with CF. Although the results of this study contradict the findings of Kazmerski et al.[28] in 2015, which associated patient knowledge and adherence in an adolescent population with CF, suggesting that patient knowledge about their disease can be an important factor in improving clinical outcomes. Overall, the studied population here had a low income, and the receipt of continuous cash benefit may have contributed to the observed better rates of TA emphasizing the importance of this financial aid in supporting the treatment of these individuals.

In 2020, Bonfim et al.[29] carried out a study to assess TA in CF at this referral center. The authors used a standardized form to calculate self-reported

TA and investigated associations with clinical and sociodemographic variables. The aforementioned study evaluated the same population; however, over the years, there have been some changes in the population profile, such as the age. Overall, the TA rate in the previous study was higher than the one obtained in this study. It is noteworthy to mention the difference in methods used to calculate self-reported TA in the studies. Possibly, lower self- reported TA rates that were observed here are, in part, due to the MGLS, which contains four questions related to the use of medication and where a positive answer already classifies the participant as non- adherent.[8] Additionally, despite limitations, the quantification of prescribed medication use, measured this study, may be more sensitive than self-report.

In Brazil, CF is contemplated by the Clinical Protocols and Therapeutic Guidelines. It was published by Ordinance Joint SAES/SCTIE/MS n. 5, 2024 April 30, including pulmonary manifestations with dornase alfa and tobramycin and pancreatic insufficiency with pancreatic enzymes. These drugs are part of the Specialized Component of Pharmaceutical Assistance, being funded by the Federal and State Governments, reaching CF patients free of charge, which can facilitate TA.[30] In addition to this facilitating factor, the dispensing of medications at the center chosen for this study takes place on the same date as the medical consultation and at the AIFC itself, optimizing the time and cost of moving individuals and their families, seeking to contribute to improving adherence. Despite the dispensing practice, the adherence rates found for all analyzed drugs were low, demonstrating the need to improve measures for improving TA in this population.

Since there is no gold-standard method for measuring adherence, a multimethod approach is needed to reduce biases and limitations.[21] It is noteworthy that the two methodologies used here are indirect. However, the Morisky-Green test, which was used to measure self-reported TA, assesses the individual's perception of treatment in a specified time, while pharmacy dispensing records are based on the dispensed amount of medication for use in a period of time, thus generating less memory bias.[9,11,21,23]

The study has some limitations: sample size, pediatric population in which the vast majority (79.1%) were below 14 years of age, and the fact that all the participants were from one single center. Records of the pharmacy dispensed drugs, as well as the MGLS, are based on reports from the participants or their caregivers and may involve memory biases, causing distortion or inaccuracy in the data. Furthermore, associations between adherence and pulmonary function were not able to be determined due to age group and the effect of COVID-19 pandemic on care. Associations between adherence and nutritional status also proved impossible to establish, since almost all the participants were adequately nourished. Despite these limitations, the study emphasizes the challenges of maintaining good TA for chronic diseases and the importance of assessing these rates and implementing continuous education programs for this population to improve TA.

In recent years, new medications, specific for individuals with certain variants in the CFTR gene, known as CFTR modulators, have emerged in the treatment of CF. In Brazil, two of these drugs have been incorporated into the Unified Health System. Despite CFTR modulators improving patient survival and well-being by partially restoring ion transport and significantly improving clinical manifestations and lung function, this therapy contributes to the expansion of the therapeutic regimen, leading to greater challenges for individuals and/or their families in maintaining good adherence.[30-32] Therefore, the challenges in maintaining adherence to symptomatic medications will be higher, requiring efforts from the healthcare team to measure and improve the adherence rates.

There is a scarcity of studies about adherence to treatment in individuals with CF in Brazil, which is a subject that merits greater attention. Further studies should be conducted to measure adherence and the factors associated with it to determine possible predictors related to adherence. This would enable the planning of strategies such as health education, supplying knowledge to patients and their families according to their needs, providing information on the disease and its progression, and offering guidance on the correct administration of prescribed medicine and the impact of correct use on the health of individuals with CF. Such interventions will likely have a positive effect on adherence-related behavior,

thus contributing to improving prognosis and consequently increasing both expectancy and quality of life.

Conclusion

The rates of good TA were low in both methods and varied depending on the medication and the methodology used. The TA concurrence between the methodologies ranged from 64% to 85.7%, with the lowest concurrence for the use of pancreatic enzymes and the highest for the use of dornase alfa. Self-reported TA for pancreatin was higher than that for inhaled medications. Pharmacy dispensation records revealed higher TA rates for inhaled medications. Good AT was mainly associated with younger participant age and lower education level of the caregiver. Complexity and long daily executing prescribed therapeutic regimen are big challenges which create significant barriers to TA.

Declaration of approval by the Research Ethics Committee
This research constitutes an extension of the project entitled "Evaluation of Treatment Adherence in Children and Adolescents with Cystic Fibrosis in a Multidisciplinary Care Center", previously approved by the Research Ethics Committee of the Professor Edgard Santos University Hospital (CEP-HUPES), under opinion no. 843,869, dated October 23, 2014. Subsequent amendments were approved under CAAE no. 3,138,374 and 4,172,628 in February 2019 and July 2020, respectively (ANNEXES A, B and C).

Acknowledgements
The authors would like to thank all the patients and their families who contributed to the present study.

Authors' contributions
FMF and ELDS: Study design, data analysis. FMF, LSV, and JCB: data collection. LSV, ABF, JCB: data analysis. ABF, JCB, MCAT, and ELDS: manuscript writing. ELDS: manuscript review.

Conflict of interest
There is no conflict of interest.

Funding
This study was partially funded by PPSUS under project 020/2013.

Data availability statement
The underlying data related to the publication will be available upon formal request to the authors.

Responsible Editor
Lindemberg Assunção Costa

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