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Research Article



Assessment of Medication Adherence and Related Factors in Children and Adolescents with Cystic Fibrosis: A Pharmacist-Led Study

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Abstract

Background: Medication non-adherence in cystic fibrosis (CF) can lead to reduced drug efficacy and suboptimal care.

Objectives: This study aimed to evaluate adherence to commonly used medications and related factors among children and adolescents with CF.

Methods: A research pharmacist assessed drug adherence using the 5-item Medication Adherence Rating Scale (MARS-5) through face-to-face interviews with patients and their parents. Based on the MARS-5 score, patients were categorized as having perfect (\geq 25) or lower (< 25) treatment adherence.

Results: A total of 300 patients were included in the study. Between 42.0% and 87.9% of patients were lower-adherent in at least one aspect of their treatment. Among those who received all medications, 86.9% were lower-adherent. Specifically, 42.0% of patients had lower adherence to inhalants, 67.6% to systemic antibiotics, 81.4% to gastrointestinal agents, and 87.9% to nutritional supplements. Factors significantly associated with adherence included the number of drugs for inhalants and systemic antibiotics; the mother's education level for inhalants, systemic antibiotics, and gastrointestinal agents; and distance from the medical center for inhalants and nutritional supplements (all P < 0.05).

Conclusions: Non-adherence to inhalants, systemic antibiotics, gastrointestinal agents, and nutritional supplements is common among children and adolescents with CF. Adherence to one class of medication does not predict adherence to others. A high number of drugs, a low mother's education level, and a long distance from the medical center decrease the likelihood of perfect adherence to CF medications.

Keywords: Compliance, Pediatrics, Pharmacist, Cystic Fibrosis (CF), Medication Adherence Rating Scale (MARS)

1. Background

Cystic fibrosis (CF) is an autosomal recessive disorder and the most common fatal inherited disease among whites, affecting multiple organ systems, including the respiratory tract, pancreas, reproductive, and digestive systems (1, 2). The CF treatment is complex and requires continuous, lifelong care at home with polypharmacy, including pancreatic enzymes, vitamins or nutritional supplements, mucolytics, bronchodilators, nebulizers, systemic antibiotics, anti-inflammatory agents, and drugs for associated conditions or complications (3). Treatment adherence is essential in chronic disease therapies to maintain health and life expectancy, although it is often reported to be low (4). Previous reports indicate that overall adherence in children with CF is approximately 50% (5). Non-adherence has been associated with faster disease progression, incorrect assessments of treatment effectiveness, increased risk for infections and hospitalization, reduced quality of life, and increased costs (6, 7). Proper use of medications directly enhances treatment efficacy and better control of symptoms such as night attacks, cough, and weight gain (7, 8).

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Medication adherence in CF is a complex issue influenced by various factors. Patient characteristics (e.g., gender, age, ethnicity, body weight, height), family and parental factors (e.g., parents' level of education, socioeconomic status, living location), and clinical factors (e.g., duration and severity of disease) are potential predictors of adherence (9-12). Factors such as the complexity of medication regimens requiring frequent daily dosing schedules, type, and number of medications can also affect patient compliance (13). Identifying adherence rates and determining barriers to medication adherence are necessary for clinicians to provide appropriate interventions.

The exact prevalence and characteristics of CF in Iran, with its Caucasian population, are unknown. UNICEF estimates that 1800 children living with CF are registered with the Ministry of Health and receive treatment (14, 15). Although numerous studies have been published on CF treatment adherence and related factors in the United States and Europe, there is a lack of data on this subject in patients with CF in Iran.

2. Objectives

This study aimed to evaluate adherence to medication regimens among children and adolescent patients with CF at a main CF center in Iran and investigate the factors affecting adherence rates.

3. Methods

3.1. Study Design and Setting

This cross-sectional study was conducted from September 2016 to October 2017 on pediatric patients with CF who were registered and attended the CF Clinic of Children's Medical Center Hospital, the main referral CF center in Iran, affiliated with Tehran University of Medical Sciences (TUMS), Tehran, Iran. The dedicated staff of this clinic includes pediatric pulmonologists, nurses, dietitians, genetic counselors, physiotherapists, respiratory therapists, and social workers. The University Review Board/University Research Council of Islamic Azad University Tehran Medical Sciences reviewed and approved both the research and ethical aspects of this study (approval number 22510303952134).

3.2. Participants

Patients with a confirmed diagnosis of CF who received at least one medication were eligible for enrollment. The exclusion criterion was refusal to participate. Written consent was obtained from parents after a full explanation of the study. Characteristics including age, sex, ethnicity, body weight, height, time of CF diagnosis, number and frequency of physician visits, any underlying diseases, list of medications, geographic area of residence, and parents' education level were recorded by a research pharmacist through face-to-face interviews with the patient in the presence of their parents. The pharmacist asked the questions and recorded the responses indicated by the respondents.

3.3. Assessment of Adherence

The 5-item Medication Adherence Rating Scale (MARS-5) questionnaire, validated in Persian (16), was used to assess adherence to commonly used medication categories in CF patients, including inhalants, systemic antibiotics, gastrointestinal agents, and nutritional supplements. The MARS-5 consists of 5 items describing non-adherent behaviors (changing dosage, forgetting to take medication, stopping medication, skipping a dose, taking less than prescribed). Patients were asked to evaluate how often they engaged in each behavior using a 5-point scale, ranging from "always" to "never" (1 - 5 points). The total scale score ranged from 5 (indicating lowest adherence) to 25 (indicating maximal adherence compliance). Patients with a MARS-5 score of 25 were categorized as having perfect treatment adherence, while those with a score of less than 25 were classified as having lower treatment adherence.

3.4. Statistical Analysis

Descriptive statistics were expressed using frequency and percentage for categorical variables and mean, standard deviation (SD), median, and interguartile range (IQR) for continuous variables. The chi-square test or Fisher exact test was used to evaluate homogeneity between the two groups of treatment adherence (lower/perfect) for qualitative variables, and Student's ttest (in the case of normality) or Wilcoxon rank-sum test (in the case of skewness) was used for continuous variables. Binary logistic regression was performed to assess the effect of several factors on the likelihood of achieving perfect treatment adherence, estimating unadjusted and adjusted odds ratios. The model included nine risk factors: Gender, age, number of drugs, duration of CF diagnosis, number of physician visits, mother's education level, father's education level, distance from the medical center, and body weight. Variables that were statistically significant in the univariable logistic regression analyses with P < 0.2were entered into a multivariable logistic regression analysis as initial risk factors. These were then analyzed by multivariable logistic regression to measure the

adjusted effect of risk factors on perfect treatment adherence. Statistical significance was considered as a two-sided P-value less than .05. All statistical analyses were performed using Stata 11.2 for Windows (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

4. Results

4.1. Patients' Characteristics

A total of 300 patients were enrolled, with no exclusions from the study. Most patients were male (58.67%) and aged between 1 month and 10 years (67%). Twenty-five percent of patients took more than five drugs, while 75% took five or fewer drugs. A total of 72.67% had been diagnosed with CF for up to 5 years, whereas 27.33% had been diagnosed for more than 5 years. Seventy-two percent had physician visits two times or fewer per year, and 60.67% resided in the province where the CF center was located (Tehran). For about half of the patients, the parents' education level was illiterate (50% for mothers and 53.67% for fathers). Inhalants were prescribed for 98.33% of patients, systemic antibiotics for 83.33%, gastrointestinal agents for 80.66%, and nutritional supplements for 85.66%. Table 1 summarizes the characteristics of all patients.

4.2. 5-Item Medication Adherence Rating Scale Score and Level of Medication Adherence

The overall mean score of the MARS-5 for all medications was 17.20 \pm 5.52. The median MARS-5 score for each medication category was as follows: 25.00 (IQR, 21.00 - 25.00) for inhalants, 21.00 (IQR, 17.00 - 25.00) for systemic antibiotics, 17.00 (IQR, 9.00 - 21.00) for gastrointestinal agents, and 17.00 (IQR, 5.00 - 21.00) for nutritional supplements. Between 42.03% and 87.94% of patients with CF were lower-adherent in at least one portion of their treatment plan. Additionally, among those who received all medications, 86.91% were loweradherent. Specifically, 42.03% of patients had lower adherence to inhalants, 67.60% to systemic antibiotics, 81.40% to gastrointestinal agents, and 87.94% to nutritional supplements. The classification of adherence to all four medication categories is shown in Figure 1.

4.3. Factors Associated with Medication Adherence

Comparison of patients' characteristics in terms of adherence to all four medication categories is shown in Table 2. Gender and the number of physician visits were the two characteristics not statistically associated with adherence levels to all four medication categories (all P 0.05). For inhalant medications, all other > characteristics were statistically related and associated with adherence levels (all P < 0.05). Duration of CF diagnosis, age (as a continuous variable), and body weight were the three characteristics not statistically associated with adherence levels to systemic antibiotic medications (P = 0.055, 0.064, and 0.267, respectively). In contrast, the other characteristics were related (all P < 0.05). The number of drugs, duration of CF diagnosis, mothers' and fathers' education, and age (as a continuous variable) were the characteristics that differed between adherence levels in gastrointestinal agents (all P < 0.05). For nutritional supplements, except for age (as a categorical variable) and the two aforementioned characteristics, all other factors varied between adherence levels (all P < 0.05).

Results of univariable (unadjusted) and multivariable (adjusted) logistic regression models assessing the likelihood of perfect adherence to all four medication categories are shown in Table 3. Any variables with P < 0.2 in univariable models were considered potential factors for predicting the likelihood of perfect adherence in each medication category. Age as a categorical variable was not included in all modeling processes due to estimation restrictions.

4.4. Inhalants

All factors were entered into the multivariable model except for gender (P > 0.2) for inhalants. Among the other factors entered, only the number of drugs, the mother's education, and distance to the medical center were statistically significant predictors of perfect adherence, controlling for all other factors in the model. Taking more than 5 drugs per day compared to 5 or fewer drugs decreased the likelihood of perfect adherence by approximately 68% (odds ratio [OR], 0.32; 95% CI, 0.15 - 0.69; P = 0.004). High school education of patients' mothers increased the likelihood of perfect adherence more than twofold compared with mothers who were illiterate (OR, 2.31; 95% CI, 1.14 - 4.66; P = 0.019), and university education of patients' mothers approximately tripled the likelihood of perfect adherence compared to illiterate mothers (OR, 2.99; 95% CI, 0.88 - 10.14; P = 0.079). Living outside Tehran province also reduced the likelihood of perfect adherence by up to 50% (OR, 0.50; 95% CI, 0.29 - 0.89; P = 0.017).

4.5. Systemic Antibiotics

In the context of systemic antibiotic medication, only the number of drugs and a mother's education among the seven potential factors were statistically significant

Table 1. General Characteristics of Participants (N = 300)	
Factors and Categories	Values ^a
Gender	
Female	124 (41.33)
Male	176 (58.67)
Age (y)	
0.08 - 10	201(67.00)
10 - 18	79 (26.33)
18 - 25	20 (6.67)
Number of drugs	
≤5	225 (75.00)
>5	75 (25.00)
Duration of CF diagnosis (y)	
≤5	218 (72.67)
> 5	82 (27.33)
Number of physician visits	
≤Twice a year	216 (72.00)
> Twice a year	84 (28.00)
Mother's education levels	
Illiterate	150 (50.00)
High school diploma	121 (40.33)
University education	29 (9.67)
Father's education levels	
Illiterate	161 (53.67)
High school diploma	115 (38.33)
University education	24 (8.00)
Distance to medical center	
Tehran province	182 (60.67)
Outside of Tehran	118 (39.33)
Medication	
Inhalant	295 (98.33)
Systemic antibiotic	250 (83.33)
Gastrointestinal agent	242 (80.66)
Nutritional supplement	257 (85.66)
Age (y)	7 (3 - 11.5)
Weight (kg)	18.75 (11 - 27)
Height (cm)	112 (88 - 137)

Abbreviation: CF, cystic fibrosis.

^a Values are expressed as No. (%) or median (interquartile range).

predictors of perfect adherence. Taking more than 5 drugs per day compared to 5 or fewer drugs reduced the likelihood of perfect adherence by approximately 88% (OR, 0.12; 95% CI, 0.15 - 0.69; P < 0.0001). Compared with mothers who were illiterate, mothers with a high school education increased the likelihood of perfect adherence by more than two and a half times (OR, 2.64; 95% CI, 1.19 - 5.87; P = 0.017), and mothers with a university education improved the likelihood of perfect adherence by more than four times (OR, 4.23; 95% CI, 1.16 - 15.43; P = 0.029).

4.6. Gastrointestinal Agents

In the context of gastrointestinal agents, the mother's education is the only robust, statistically significant predictor of perfect adherence. Compared to mothers who were illiterate, mothers with a high school education significantly increased the likelihood of perfect adherence (OR, 5.95; 95% CI, 2.17 - 16.36; P = 0.001), and mothers with a university education further



Figure 1. Classification of adherence to commonly used medications

improved the likelihood of perfect adherence (OR, 8.33; 95% CI, 2.04 - 34.05; P = 0.003).

4.7. Nutritional Supplements

Distance to the medical center is the only statistically significant predictor of perfect adherence to dietary supplements and medications. Results of the adjusted model indicate that living outside of Tehran decreases the likelihood of perfect adherence by up to 81% (OR, 0.19; 95% CI, 0.05 - 0.73; P = 0.015).

5. Discussion

Medication adherence in CF, a lifelong disease with complex, costly, and time-consuming treatment, is crucial. To the best of our knowledge, this is the first study to evaluate medication adherence and associated factors in Iranian patients with CF. Our findings showed low adherence to commonly used medications in approximately 87% of children and adolescent patients with CF. A targeted literature review by Narayanan et al. assessed 19 published studies from 2010 to 2016 on adherence rates to different CF treatments and demonstrated that adherence to CF therapies is moderate-to-low (suboptimal) and varies significantly by treatment type, mode of treatment administration, method of adherence measurement, and also by age, season, and time (17). Later studies also confirm the findings of low adherence to medical treatment in CF patients (18, 19).

Among the commonly used medication classes in CF, inhalants, the most used medications in studied patients (in more than 98%), had the highest adherence rate (\sim 58% with perfect adherence). In contrast, nutritional supplements had the lowest adherence (\sim 12% with perfect adherence). Higher adherence to respiratory tract medications (i.e., inhalants and systemic antibiotics) in studied patients may be

explained by the fact that pulmonologists run the CF Clinic in Iran, and CF is also known as a lung disease to most people. Therefore, patients and their parents may be more likely to adhere to medications targeting the lung. Studies on pancreatic enzyme replacement therapy or vitamins also showed much lower adherence levels than some inhaled therapies and antibiotics (6, 20, 21). It should be noted that among patients with CF, adherence to one class of medication cannot predict adherence to other medication classes, as reported by similar studies.

This study found that perfect medication adherence in children with CF was associated with the number of drugs, the mother's education level, and distance from the medical center. Specifically, taking more than five drugs per day decreases the likelihood of perfect adherence to inhalants and systemic antibiotics. The high school and university education level of patients' mothers increases the likelihood of perfect adherence compared with illiterate mothers for inhalants, systemic antibiotics, and gastrointestinal agents. Living outside of Tehran province decreases the likelihood of perfect adherence to inhalants and nutritional supplements. A high level of polypharmacy (i.e., an increased number of treatments taken each day) is identified as a barrier to adherence (5, 6). However, similar to our results, Zindani et al. did not find a significant correlation between the total number of medications and adherence to dornase alfa or multivitamins in CF patients (11). Mothers' university education positively affected adherence to inhalants, systemic antibiotics, and gastrointestinal agents. Previous studies have shown that children of parents with lower educational attainment are less adherent to medications for chronic diseases like attention deficit hyperactivity disorder (ADHD), glaucoma, and transplant (22-24). Besides the psychological status of the parents, the level of stress of the patient and parents is involved in medication adherence (25). Management of parent behaviors, such as parent training, is known to promote adherence among chronically ill youth (26). Therefore, future research on improving a mother's knowledge may be crucial for better medication adherence in pediatric patients with CF. Living far from the medical center was another predictor of adherence for inhalants and nutritional supplements. In a study evaluating the effects of distance traveled on adherence to treatment, families who lived more than 20 miles from a pediatric dermatology clinic were more likely to be non-adherent to the treatment plan (27). This highlights the need to increase the number of pediatric

medical centers across the country, particularly in underserved areas.

The researchers observed no significant correlation between adherence to commonly used medications and the patient's gender, age, body weight, father's education level, number of physician visits, and disease duration. Various studies investigating barriers influencing adherence to CF therapies have yielded contradictory results. Although several previous studies have demonstrated that treatment adherence decreases with advancing age, disease severity, and long disease duration, others found no significant relationship (12, 18, 20, 21, 28, 29).

Several direct and indirect methods have been used to determine patients' medication adherence in CF. Among them, the Medication Adherence Rating Scale (MARS) describes an individual's medication adherence by evaluating attitudes about medications and actual medication-taking behavior (30). Using the MARS-5 questionnaire in this study as an objective measurement tool appears to be a more reliable and valid method for estimating compliance — rather than using self-report methods — by having the researcher read and explain the questions to the patients and parents.

5.1. Study Limitations

The major limitation of the present study is the lack of evaluation of the impact of adherence rates on clinical outcomes. The relationship between low adherence to medication and clinical variables with larger sample sizes from multicenter studies is needed to elucidate the complex relationships between adherence to treatment and various aspects of CF management. Moreover, additional factors such as parental age and the socioeconomic status of patients can be considered as influencing factors of medication adherence in future studies.

5.2. Conclusions

Non-adherence to inhalants, systemic antibiotics, gastrointestinal agents, and nutritional supplements is common in children and adolescents with CF, and adherence to one class of medication cannot predict adherence to others. Taking more than five drugs is associated with lower adherence to inhalants and systemic antibiotics. Additionally, living far from the medical center is related to lower adherence to inhalants and nutritional supplements. Conversely, a high education level of patients' mothers increases the likelihood of perfect adherence to inhalants, systemic antibiotics, and gastrointestinal agents. Educational interventions with planned patient monitoring may be needed to improve medication adherence in the pediatric CF population.

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Footnotes

Authors' Contribution: Study concept and design: A. Sh. and H. E.; Collection and interpretation of clinical data: R. S.; Analysis and interpretation of data: K. A. and Sh. B.; Drafting of the manuscript: Sh. M.; Critical revision of the manuscript for important intellectual content: A. Sh. and Sh. B.; Statistical analysis K. A.

Conflict of Interests Statement: The authors declared no conflict of interests.

Data Availability: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to some limitation in their containing information that could compromise the privacy of research participants.

Ethical Approval: 22510303952134

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Informed Consent: Written consent was obtained from parents after a full explanation of the study.

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Medication. Associated Factors and Categories	Lower Treatment Adherence	Perfect Treatment Adherence	P.Value
Inhalants	Lower neutricin/hancrence	reneer neutricite Autorenee	1-value
Total	124 (42.03)	171 (57.97)	
Gender			0.681
Female	53 (42.74)	69 (40.35)	
Male	71 (57.26)	102 (59.65)	
Age			0.001
0.08-10	73 (58.87)	128 (74.85)	
10-18	12 (9.68)	40 (25.59) 3 (175)	
Number of drugs	a (3000)	5(005)	< 0.0001
≤5	73 (58.87)	149 (87.13)	
>5	51 (41.13)	22 (12.87)	
Duration of CF diagnosis (y)			0.001
≤5	77 (62.10)	137 (80.12)	
>5	47 (37.90)	34 (19.88)	
Number of physician visits	0.5 (88.40)	415 (CB 05)	0.056
≤ IWICE a year	96 (77.42)	115 (67.25)	
Mother's education levels	20(22.30)	50 (32.75)	< 0.0001
Illiterate	83(66.94)	63 (36.84)	
High school diploma	34 (27.42)	86 (50.29)	
University education	7 (5.65)	22 (12.87)	
Father's education levels			0.002
Illiterate	81 (65.32)	76 (44.44)	
High school diploma	37 (29.84)	78 (45.61)	
University education	6 (4.84)	17 (9.94)	
Distance to medical center	52 (22.24)		0.001
Ienran province	63 (50.81)	119 (69:59)	
Are	61 (49.19)	52 (30.41)	h
Age	8.5 (5 - 12)	5(1-10)	< 0.0001
Weight	21.5 (14.25 - 32)	15 (10 - 23)	< 0.0001 ^b
Systemic antibiotic			
Total	169 (67.60)	81(32.40)	
Gender	75 (44.28)	20 (27.04)	0.271
Male	/3 (44.36)	50 (57.04)	
Ασρ	54(33.02)	51(02.50)	0.009
0.08-10	101 (59.76)	53 (65.43)	01005
10 - 18	50 (29.59)	28 (34.57)	
18 - 25	18 (10.65)	0 (0.00)	
Number of drugs			< 0.0001
≤5	103 (60.95)	75 (92.59)	
>5	66 (39.05)	6 (7.41)	
Duration of CF diagnosis (y)	100 (7 1 50)	(a) (a) a)	0.055
55 57	109 (64.50)	b2(/b.54) 10(22.45)	
Number of physician visits	00(35.50)	19 (25.40)	0.163
≤2 times a year	125 (73.96)	53 (65.43)	
> 2 times a year	44 (26.04)	28 (34.57)	
Mother's education levels			< 0.0001
Illiterate	105 (62.13)	25 (30.86)	
High school diploma	54 (31.95)	41 (50.62)	
University education	10 (5.92)	15 (18.52)	
Father's education levels		11 (11 m A	0.003
Illiterate	107 (63.31)	33 (40.74)	
High school diploma	51 (30.18)	40 (49.38) 8 (9.88)	
Distance to medical center	1(0.5)	6(3.00)	0.402
Tehran province	97 (57.40)	51(62.96)	0.102
Outside of Tehran	72 (42.60)	30 (37.04)	
Age	8 (5-12)	7(4-11)	0.054 b
Weight	21(14-22)	10 5 (12 - 27)	0.004
Castrointectinal agents	21(14-52)	193 (15-27)	0.267
Total	197 (81 40)	45 (18 60)	-
Gender	157 (6116)	15(16666)	0.668
Female	85(43.15)	21(46.67)	0.000
Male	112 (56.85)	24 (53.33)	
Age			0.328
0.08 - 10	129 (65.48)	34 (75.56)	
10 - 18	64 (32.49)	11 (24.44)	
18 - 25	4 (2.03)	0 (0.00)	
Number of drugs	·····		0.002
≤5	139 (70.56)	42 (93.33)	
>5 Duration of CE diagraphic (v)	58 (29.44)	3 (6.67)	0.021
<5	127 (64 47)	39 (86.67)	0.004
>5	70 / 25 52 \	6 (12 22)	
Number of physician visits	/0(30.30)	(66.61) 0	0.147
≤ 2 times a year	144 (73.10)	28 (62.22)	0.147
> 2 times a year	53 (26.90)	17 (37.78)	
Mother's education levels			< 0.0001
Illiterate	116 (58.88)	8 (17.78)	

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Medication, Associated Factors and Categories	Lower Treatment Adherence	Perfect Treatment Adherence	P-Value
High school diploma	64 (32.49)	28 (62.22)	
University education	17 (8.63)	9 (20.00)	
Father's education levels			0.010
Illiterate	119 (60.41)	16 (35.56)	
High school diploma	65 (32.99)	24 (53.33)	
University education	13 (6.60)	5 (11.11)	
Distance to medical center			0.093
Tehran province	118 (59.90)	33 (73.33)	
Outside of Tehran	79 (40.10)	12 (26.67)	
Age	8 (4 -11)	5(2-9)	0.007 ^b
Weight	19.8 (13.5 - 24.5)	16 (10.5 - 27.5)	0.106 ^b
Nutritional supplements			
Total	226 (87.94)	31 (12.06)	
Gender			0.880
Female	98 (43.36)	13 (41.94)	
Male	128 (56.64)	18 (58.06)	
Age			0.068
0.08-10	151 (66.81)	27(87.10)	
10 - 18	71 (31.42)	4 (12.90)	
18 - 25	4 (1.77)	0 (0.00)	
Number of drugs			0.018
≤5	168 (74.34)	29 (93.55)	
> 5	58 (25.66)	2(6.45)	
Duration of CF diagnosis (y)			0.037
≤5	156 (69.03)	27 (87.10)	
> 5	70 (30.97)	4 (12.90)	
Number of physician visits			0.893
≤ 2 times a year	163 (72.12)	22 (70.97)	
> 2 times a year	63 (27.88)	9 (29.03)	
Mother's education levels			0.003
Illiterate	118 (52.21)	7 (22.58)	
High school diploma	88 (38.94)	17 (54.84)	
University education	20 (8.85)	7 (22.58)	
Father's education levels			0.001
Illiterate	129 (57.08)	7 (22.58)	
High school diploma	82 (36.28)	20 (64.52)	
University education	15 (6.64)	4 (12.90)	
Distance to medical center			0.001
Tehran province	135 (59.73)	28 (90.32)	
Outside of Tehran	91 (40.27)	3 (9.68)	
Age	7 (3 -11)	0.91(0.67-5)	< 0.0001 ^b
Weight	19 (12 - 26)	9.8 (6.7 - 16)	< 0.0001 ^b

Abbreviations: IQR, interquartile range; CF, cystic fibrosis.

^a Values are expressed as No. (%) or median (IQR).

^b Based on Wilcoxon rank-sum (Mann-Whitney) test; All other P-values are based on the chi-square test.

	Univariable M	odel	Multivariable Mode	el
Medication, Associated Factors and Categories	Raw OR (95%CI)	P-Value	Adjusted OR (95%CI)	P-Value
Inhalants				
Gender				
Female	Ref.	-	Ref.	-
Male	1.10 (0.69 - 1.76)	0.681	-	•
Age Number of drugs	0.91(0.87-0.95)	< 0.0001	1.03 (0.91 - 1.17)	0.663
<pre>s5</pre>	Ref.	-	Ref.	
~5	0.21 (0.12 - 0.37)	< 0.0001	0.32 (0.15 - 0.69)	à
Putation of CE discoverie (c)	0.21(0.12-0.37)	< 0.0001	0.52 (0.15 - 0.03)	0.004 "
< 5	Ref		Ref	
>5	0.41(0.24-0.59)	0.001	0.75 (0.38 - 1.50)	0.418
Number of physician visits	0.11(0.24 0.05)	0.001	0.75(0.50 1.50)	0.110
≤ 2 times a year	Ref.		Ref.	
> 2 times a year	1.67 (0.98 - 2.83)	0.057	1.17 (0.63 - 2.17)	0.622
Mother's education levels				
Illiterate	Ref.	-	Ref.	•
High school diploma	3.33 (1.99 - 5.58)	< 0.0001	2.31 (1.14 - 4.66)	0.019 ^a
University education	4.14 (1.66 - 10.30)	0.002	2.99 (0.88 - 10.14)	0.079
Father's education levels				
Illiterate	Ref.	-	Ref.	-
High school diploma	2.25 (1.36 - 3.71)	0.002	1.24 (0.62 - 2.48)	0.540
University education	3.02 (1.13 - 8.06)	0.027	1.00 (0.28 - 3.65)	0.995
Ulstance to medical center			D -5	
ienran province	Ret.	-	Ret.	
	0.45 (0.28 - 0.73)	0.001	0.50 (0.29 - 0.89)	0.017 4
weight Sustamic antibiotic	0.96 (0.95 - 0.98)	< 0.0001	0.97(0.92-1.03)	0.314
Systemic antibiotic				
Female	Dof		Ref	
Male	125 (0.79 - 2.24)	0.272	ici.	-
Age	0.94 (0.89 - 0.99)	0.021	1.01 (0.87 - 1.17)	0,914
Number of drugs				
≤5	Ref.	-	Ref.	-
> 5	0.12 (0.05 - 0.30)	< 0.0001	0.12 (0.04 - 0.37)	< 0.0001 ^a
Duration of CF diagnosis (y)				1010001
≤5	Ref.	-	Ref.	-
>5	0.56 (0.30 - 1.02)	0.057	0.80 (0.37 - 1.76)	0.583
Number of physician visits				
≤ 2 times a year	Ref.	-	Ref.	•
> 2 times a year	1.50 (0.85 - 2.66)	0.164	0.94 (0.47 - 1.88)	0.858
Mother's education levels				
lliiterate	Ref.		Ref.	
High school diploma	3.19 (1.76 - 5.79	< 0.0001	2.64 (1.19 - 5.87)	0.017 ^a
University education	6.30 (2.53 - 15.67)	< 0.0001	4.23 (1.16 - 15.43)	0.029 ^a
Father's education levels				
Illiterate	Ref.	-	Ref.	•
High school diploma	2.54 (1.44 - 4.49)	0.001	1.36 (0.62 - 2.99)	0.443
University education	2.36 (0.88 - 6.35)	0.090	0.78 (0.21 - 2.92)	0.717
Distance to medical center	- 1			
Tehran province	Ref.		Ref.	•
Outside of Jenran Weight	0.22 (0.46 - 1.37)	0.402	-	-
weight Castrointectinal Agents	0.98 (0.96 - 1.00)	0.091	1.01(0.95-1.08)	0.752
Gender				
Female	Ref.	· ·	Ref.	
Male	0.87 (0.45 - 1.66)	0.668	•	
Age	0.90 (0.83 - 0.97)	0.009	0.98 (0.88 - 1.09)	0.683
Number of drugs				
≤5	Ref.	-	Ref.	
> 5	0.17 (0.05 - 0.57)	0.004	0.39 (0.1 - 1.55)	•
Duration of CF diagnosis (y)				
≤5	Ref.	-	Ref.	-
> 5 Number of physician visits	0.28 (0.11 - 0.69)	0.006	0.36 (0.11 - 1.12)	0.077
≤2 times a year	Ref	-	Ref	-
> 2 times a year	165(0.84-3.26)	0.149	116(0.52-2.58)	0.181
Mother's education levels	103(004 340)	5445		0.101
Illiterate	Ref.	-	Ref.	-
High school diploma	6.34 (2.73 - 14.74)	< 0.0001	5.95 (2.17 - 16.36)	0.001 a
	768(361, 3360)	< 0.0001	8 22 (2 04 24 05)	0.001
Extraction levels	7.68 (2.61 - 22.60)	< 0.0001	8.33 (2.04 - 34.05)	0.003
raciel s'education reveis	n «f		Dof	
High school diploma	2 75 (1 26 - 5 54)	-	Kel. 0.93(0.27-2.21)	0.971
University education	2.75 (1.50 - 5.54) 2.86 (0.90 - 9.09)	0,075	0.59 (0.14 - 2.46)	0.473
Tehran province	Ref.	-	Ref.	-
Distance to medical center				
Outside of Tehran	0.54 (0.26 - 1.12)	0.096	0.69 (0.30 - 1.59)	0.385
Weight	0.98 (0.95 - 1.01)	0.233	-	-
Nutritional supplements				
Gender				

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Medication, Associated Factors and Categories	Univariable M	Univariable Model		Multivariable Model	
	Raw OR (95%CI)	P-Value	Adjusted OR (95%CI)	P-Value	
Female	Ref.		Ref.		
Male	1.06 (0.50 - 2.27)	0.880			
Age	0.79 (0.70 - 0.88)	< 0.0001	0.87 (0.63 - 1.20)	0.393	
Number of drugs					
≤5	Ref.		Ref.	-	
> 5	0.20 (0.05 - 0.86)	0.031	0.71 (0.13 - 3.91)	0.690	
Duration of CF diagnosis (y)					
≤5	Ref.	-	Ref.	-	
>5	0.33 (0.11 - 0.98)	0.046	2.23 (0.44 - 11.27)	0.333	
Number of physician visits					
≤ 2 times a year	Ref.		Ref.		
> 2 times a year	1.06 (0.46 - 2.42)	0.893			
Mother's education levels					
Illiterate	Ref.		Ref.		
High school diploma	3.26 (1.29 - 8.19)	0.012	1.15 (0.36 - 3.71)	0.817	
University education	5.90 (1.87 - 18.63)	0.002	3.67 (0.79 - 17.02)	0.096	
Father's education levels					
Illiterate	Ref.		Ref.		
High school diploma	4.49 (1.82 - 11.10)	0.001	2.79 (0.89 - 8.79)	0.079	
University education	4.91 (1.29 - 18.76)	0.020	2.58 (0.48 - 14.03)	0.271	
Distance to medical center					
Tehran province	Ref.	•	Ref.	-	
Outside of Tehran	0.16 (0.05 - 0.54)	0.003	0.19 (0.05 - 0.73)	0.015 ^a	
Weight	0.91 (0.86 - 0.96)	< 0.0001	0.94 (0.83 - 1.08)	0.406	

Abbreviations: CF, cystic fibrosis; OR, odds ratio.

^a Was considered statistically significant.