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Treatment Complexity in Cystic Fibrosis: Trends over Time and Associations with Site-Specific Outcomes

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Abstract

Background—Patients with cystic fibrosis (CF) have increasing treatment complexity and high treatment burden. We describe trends in treatment complexity and evaluate its relationship with health outcomes.

Methods—Using Epidemiologic Study of Cystic Fibrosis (ESCF) data, we developed a treatment complexity score (TCS) from 37 chronic therapies and assessed change by age group (6–13, 14–17, and 18+ years) over a three year period. Differences in average site TCS were evaluated by quartiles based on FEV1, BMI, or Treatment Burden score on the Cystic Fibrosis Questionnaire-Revised (CFQ-R).

Results—TCS scores were calculated for 7252 individual patients (42% child, 16% adolescent, 43% adult) across 153 sites. In 2003, mean TCS was 11.1 for children, 11.8 for adolescents, and 12.1 for adults. In all 3 age groups, TCS increased over 3 years; the increase in TCS from 2003–2005 for children was 1.25 (95% CI 1.16–1.34), for adolescents 0.77 (0.62–0.93), and for adults 1.20 (1.08–1.31) (all $p<0.001$ for trend over time). At the site level, there were no significant differences in mean TCS based on FEV_1 quartile. Mean TCS was higher in the highest BMI z-

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Disclosure of Conflict of Interest

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score quartile. Across all 3 versions of the CFQ-R, mean TCS was lower at sites in the highest quartiles (lowest burden) for CFQ-R Treatment Burden scores.

Conclusion—Treatment complexity was highest among adults with CF, although over 3 years, we observed a significant increase in treatment complexity in all age groups. Such increases in treatment complexity pose a challenge to patient self-management and adherence. Future research is needed to understand the associations between treatment complexity and subsequent health outcomes to reduce treatment burden and improve disease management.

INTRODUCTION

Over the past several decades, improvements in the management of cystic fibrosis (CF) have led to significant increases in patient survival and quality of life.[1] Treatment guidelines for respiratory medications in CF recommend a number of chronic maintenance treatments, including bronchodilators, mucolytics, inhaled antibiotics, anti-inflammatories, and airway hydrators.[2] In addition, a vigorous airway clearance regimen and regular exercise are recommended for most patients with CF.[3] This treatment regimen is both time-consuming and complex, requiring use of specific devices, such as inhalers or nebulizers, with varying administration and cleaning times. Beyond pulmonary care, most individuals with CF require additional therapies, such as pancreatic enzyme replacement. As a result, the treatment burden for patients with CF is high, with estimates suggesting the regimen takes two to three hours per day for routine CF care.[4] Adherence to CF treatment regimens is often poor, generally 50% or less to prescribed therapies.[5–7] The high treatment burden in CF may impede efforts to improve adherence to daily therapies and consistency among health care practitioners in the implementation of chronic care guidelines.

Published data on treatment burden in CF exists for adults,[4] but there is a paucity of evidence on whether a similar treatment burden exists for children and adolescents. A recent analysis of longitudinal data from the Epidemiologic Study of Cystic Fibrosis (ESCF) showed that individuals of all ages with increasing treatment complexity over a one year period had worsening scores on a patient-reported outcome measure of treatment burden.[8] With early diagnosis through newborn screening and research documenting early signs of airway inflammation and infection in younger children, earlier adoption of chronic therapies is becoming a cornerstone of aggressive CF care. Prior analyses of ESCF have also shown that more aggressive care practices are associated with improved patient outcomes.[9] Introducing complex and time-consuming therapies early in life, and requiring maintenance of these regimens through adulthood, poses significant challenges to individual patient and family adherence.

The objectives of this study were 1) To evaluate CF treatment complexity in individuals over time and as a function of age and disease severity and 2) To describe differences in average site-level CF treatment complexity and to determine whether average treatment complexity was associated with site-specific health outcomes including lung function, nutritional status, and patient-reported treatment burden. We hypothesized that individual treatment complexity would increase over time, and that sites with better patient outcomes would have higher average treatment complexity.

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METHODS

Study Population

ESCF is a large multicenter, longitudinal, prospective observational study of the clinical course of patients with CF in the United States and Canada from 1994 through 2005.[10] Data collected on each patient included clinical demographics, signs and symptoms of lung disease, results of spirometry and respiratory tract cultures, and documented use of routine therapies. Quality of life data was included in ESCF starting in 2003. Informed consent was obtained according to decisions by a local or central human subjects review board (Copernicus Group tracking number OVA1-03-008). For this analysis, we used data from ESCF collected in 2003–2005. Patients needed to be ≥ 6 years in 2004 and have ≥1 encounter in 2004 and ≥1 recorded pulmonary function test in 2004.

Outcome Measures

The primary individual-level outcome assessed in this analysis was a treatment complexity score (TCS), developed by assigning a complexity of 1, 2, or 3 based on daily frequency, duration, and ease of administration of each of 37 chronic therapies captured at each ESCF encounter.[8] Oral medications and metered-dose inhalers were assigned a TCS of 1 (n=20 therapies), once-daily nebulized therapies and pancreatic enzymes a TCS of 2 (n=8 therapies), and airway clearance, twice-daily nebulized therapies, use of oxygen, CPAP, BiPAP, and insulin or enteral supplements a TCS of 3 (n=9 therapies). A composite TCS (range 0–72) was calculated as the sum of all individual scores at each encounter (Table 1). We further categorized therapies as respiratory or non-respiratory (TCS-Respiratory and TCS-Other) to develop specific subscores in these two domains.

Site-level health status outcomes included in the analyses were: 1) lung function, measured by forced expiratory volume in 1 second (FEV_1) percent predicted (Pulmonary function test results were reported as measured values and converted to percent predicted using reference equations from Wang et al. for females through age 15 and males through age 17, and Hankinson et al. at older ages)[11, 12] and 2) nutritional status, measured by body mass index (BMI) z-score. In addition, we assessed patient-reported treatment burden as measured by the Treatment Burden domain score from the Cystic Fibrosis Questionnaire-Revised (CFQ-R; Quittner et al., in press), a validated CF-specific quality of life instrument that includes teen/adult, parent, and child versions.[13, 14] Scores are standardized on a 0–100 point scale, with higher scores indicating lower Treatment Burden. For the site-level analyses, sites with fewer than 8 patients for any of the outcomes were excluded.

Statistical Analysis

We conducted two distinct analyses in this study. For the first analysis, we evaluated trends in individual TCS scores over time from 2003–2005. For this analysis, in addition to requiring lung function and nutritional data in 2004 and ≥1 encounter, we also required data on these measures in each of years 2003 and 2005. We examined changes in average TCS over 3 years from 2003–2005 stratified by age [6–13 years (child), 14–17 years (adolescent), 18+ years (adult)] and by lung function decile.[15] Individuals who switched age groups across years 2003–2005 were omitted from the trends over time analyses. The minimum,

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median, and maximum TCS were computed for each patient in each of years 2003, 2004, and 2005 and then averaged across patients for a given year. The analyses were performed using the MIXED procedure in SAS treating patient as a random effect, with ESTIMATE statements used to test for differences between the extreme quartiles and for linear trend across quartiles.

Our second analysis was a site-based analysis designed to evaluate the relationship between average site TCS scores and site-specific health outcomes. ESCF sites were stratified into quartiles based on 2004 data for mean FEV_1 (patient's best value), mean BMI z-score (patient's mean), and mean CFQ-R Treatment Burden score (patient's mean). Differences in average TCS (based on patient's median value in 2004) among quartiles were assessed using t-tests.

Statistical analyses were performed using SAS 9.2 (SAS Institute, Inc., Cary, NC). A 2-sided *P* value <.05 was considered statistically significant.

RESULTS

Over the 3 years of ESCF data collection, from 2003 to 2005, a total of 21,756 records, representing 7,252 patients, had an encounter-based TCS calculated in each year. Over this time period, the mean TCS was 12.3 ± 4.3 (inter-quartile range: 9.5 – 15.0). The major determinants of the overall TCS were respiratory therapies, as the mean TCS-Respiratory was 9.8 ± 3.4 (inter-quartile range: 8.0 – 12.0), and the mean TCS-Other was 2.4 ± 1.6 (inter-quartile range: 1.0 – 3.0). As expected there was an inverse correlation between TCS and CFQ-R Treatment Burden score which varied by age. For the adolescent (14–17) and adult (18+) patients, the correlation was −0.27. For children (age 6–13), the correlation for the child questionnaire was −0.10 and for the parent questionnaire was −0.32.

Trends Over Time Analysis

A total of 7252 patients met inclusion criteria for the trends over time analysis of TCS. Clinical and demographic characteristics are shown in Table 2. In 2003, mean TCS (based on patient median) was 11.1 for children, 11.8 for adolescents, and 12.1 for adults. In all 3 age groups, TCS increased over 3 years; in 2005, the mean TCS were 12.4, 12.6, and 13.3 respectively (all P<0.001 for trend over time). The mean increase in TCS from 2003 to 2005 for children was 1.25 (95% CI 1.16–1.34), for adolescents 0.77 (0.62–0.93), and for adults 1.20 (1.08–1.31). Mean TCS also increased in patients with more advanced lung disease (P<0.001 for trend over FEV_1). Figure 1 shows the mean TCS for each year (2003–2005) stratified by age group and lung function decile. Overall, the mean treatment complexity in all age groups was highest in patients with severe lung disease (lowest deciles). The increase in TCS over the two years was particularly pronounced among child and adolescent patients with more advanced lung disease (p<.001 for trend across deciles in TCS increase for ages 6–13 and 18+; p=0.07 for age 14–17). Adults with mild lung disease had the lowest overall mean TCS. These trends were similar when the analyses were repeated on the two components of TCS, TCS-Respiratory and TCS-Other.

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Site-Specific Quartile Analysis

Table 3 presents the mean FEV_1 % predicted, BMI z-score, and CFQ-R Treatment Burden scores in 2004 for the ESCF sites included in the site-level analysis. Patient-level demographics for the highest and lowest quartile sites for Treatment Burden among the three versions are shown in Table 4. For the child (age 6–12 years) and parent (for children age 6–12 years) CFQ-R, sites in the lowest quartile for Treatment Burden scores (i.e. those with the highest perceived treatment burden) had patients with lower mean lung function and a higher proportion of Medicaid patients. By contrast, for the teen/adult CFQ-R Treatment Burden quartiles, sites in the lowest quartile for Treatment Burden, had patients with older mean age and lower mean lung function, with no significant difference in insurance status.

Although no significant difference in mean TCS at the site level were found based on FEV_1 % predicted quartiles, differences in mean TCS based on the highest and lowest BMI z-score site quartiles were statistically significant at $p<.05$ (Figure 2), indicating that patients with better nutritional status had more complex treatment regimens. In contrast, mean treatment complexity scores were highest in sites that fell into the lowest quartile (more treatment burden) across all three versions of the CFQ-R Treatment Burden scale (Figure 3). For example, in sites with the lowest teen/adult CFQ-R Treatment Burden scores (i.e., highest burden), mean TCS was 13.4 (95% CI 13.0, 13.8) compared to a mean TCS of 12.5 (95% CI 12.1, 12.9) in the sites with the best Treatment Burden scores ($p <.05$). Statistical tests for trend over quartiles mirrored the comparisons of the upper and lower quartile.

DISCUSSION

Recommended therapies for the chronic management of CF result in a high treatment burden for individual patients. In this study, we examined treatment complexity in a large observational cohort of patients with CF over a three-year period. As expected, treatment complexity was highest among adults and those with more severe lung disease. However, over the 3-year analytic period, treatment complexity increased in all age groups and disease severity groups.

Our findings extend previous literature on treatment burden in CF by examining a larger age spectrum and by comparing treatment complexity scores to patient-reported burden. Based on existing CF chronic care guidelines, an individual patient would be expected to use at least 3–5 respiratory therapies, along with 3–5 non-respiratory therapies each day.[3] In this analysis we did not evaluate differences between an expected treatment complexity based on care guidelines and the observed treatment complexity, although future studies could consider the impact of such differences on patient outcomes. Our results suggest that patients, on average are prescribed a high intensity regimen, with children being required to perform nearly as many treatments as adults. Even in our short time window, we observed a rise in complexity over time, with the increase in complexity for children mirroring that of adolescents and adults. When assessed by lung function severity, there was no difference in treatment complexity based on age. Importantly, during the time period we analyzed, no new therapies for CF patients were introduced, indicating that these data reflect the widespread adoption of an early, aggressive approach to care, particularly for individuals with more severe disease.

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The increase in treatment complexity over time across all groups, regardless of disease severity, is statistically significant, and likely has clinical significance as well. Although the average rise in treatment complexity over the three year period is small, a similarly sustained increase over a longer time period would lead to substantial increases over the lifespan of a typical CF patient. With increased recognition that early intervention improves outcomes in CF, our observed trends likely reflect the increased introduction of maintenance therapies across CF care centers throughout the lifespan. Although such increases in treatment complexity may be needed to improve overall population health, on an individual level, they pose a challenge to patient self-management, perceived treatment burden, and adherence to chronic therapies. In our analysis, we have identified inverse correlations between treatment complexity scores and treatment burden scores. Interestingly, for younger children, this correlation of higher magnitude in the parental questionnaires, suggesting that parents and children may have differential perceptions of treatment burden. We previously reported that changes in treatment complexity over a 12 month period in a subset of ESCF data were not associated with changes in CFQ-R Treatment Burden scores in adult and adolescent patients.[8] Unfortunately, frequent longitudinal measurements of treatment burden in the same patient are not generally available in ESCF. The dynamics of perceived treatment burden over time, with and without changes in treatment complexity, would be of considerable research interest in future studies. In addition, as new therapies are developed and implemented in the care of CF patients, attention must be paid to whether continued additive therapies in the face of rising complexity could negate the impact of new therapies because of reduced adherence. Efforts to reduce complexity, via new technologies or ease of administration, should be considered in future CF drug development.[16]

Our study is the first to evaluate the relationship between treatment complexity at a site-level with health outcomes, including lung function and QOL. Earlier analyses of ESCF have identified associations between site-level markers of aggressive care, such as frequency of visits, frequency of IV and oral antibiotics, and frequency of cultures with site-level lung function.[9] We therefore hypothesized that higher quartile sites would be more aggressive with chronic therapies and have higher average TCS. However, our site-level analysis did not show a linear difference in average treatment complexity based on average site lung function. In fact, the highest average site TCS were at the highest and lower quartile sites for lung function. One potential explanation for this observed relationship is that high performing sites are more aggressive in terms of treatments, and that low performing sites are recommending more therapies as they have patient populations with increased disease severity. Overall, our data suggests that treatment intensity at the site level is likely more dependent on factors such as disease severity. Our data does not allow us to investigate the impact of aggressive care practices not captured in the TCS such as more frequent use of oral antibiotics or lower thresholds for hospitalization. In addition, frequency of routine maintenance visits and surveillance may be more variable than the recommendations for chronic medications and thus, may be more strongly associated with average site-level patient outcomes. Interestingly, we did see an association between site level nutritional status and TCS, with higher average complexity at sites with better nutritional outcomes. Perhaps these sites pay greater attention to nutrition, resulting in higher prescriptions for non-respiratory therapies.

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We also assessed patient-reported treatment burden using the CFQ-R Treatment Burden scale. At the site level, we found differences in average treatment complexity based on perceived burden, with higher average treatment complexity in sites with higher reported patient burden. These sites appear to care for sicker patients, with an older average age and a lower average lung function. Interestingly, these sites also appear to care for more disadvantaged populations, with a greater proportion of patients insured with Medicaid, a marker for socioeconomic disadvantage, at sites with higher reported treatment burden. Socioeconomic disparities in health outcomes have been described in other studies of CF patients, and our data suggests that SES factors may also be contributing to perceptions of treatment burden.[17] Overall, however, the relationship between average treatment complexity and site-level reported burden is in the expected direction, with higher complexity scores at sites with patients reporting greater burden. This suggests that monitoring patient perceived treatment burden using instruments such as the CFQ-R has potential to aid clinicians in their consideration of adding new medications, particularly in clinical care centers that recommend highly complex treatment regimens for their patients.

The major limitation of our analysis is that treatment data was obtained from encounter-based, not patient-queried reports. Thus, the treatment complexity score is a proxy for recommended therapies and not necessarily the therapies used by individual patients. Despite this limitation, the TCS could be useful in evaluating overall treatment intensity as an aid to decision-making about adding treatments to an existing complex regimen. In conclusion, in a national cohort of CF patients, we documented a substantial level of treatment complexity, which was increasing over time. Future research is needed to understand the associations between treatment complexity, adherence behavior, and subsequent health outcomes. Future work is also needed to reduce treatment burden and improve disease management and adherence, particularly in an era of novel, emerging CF therapies. Finally, treatment complexity and patient-reported treatment burden should be considered as outcome variables in comparative effectiveness studies, which are needed to develop an evidence base for clinicians and patients to make informed decisions about adding new treatments to the regimen.

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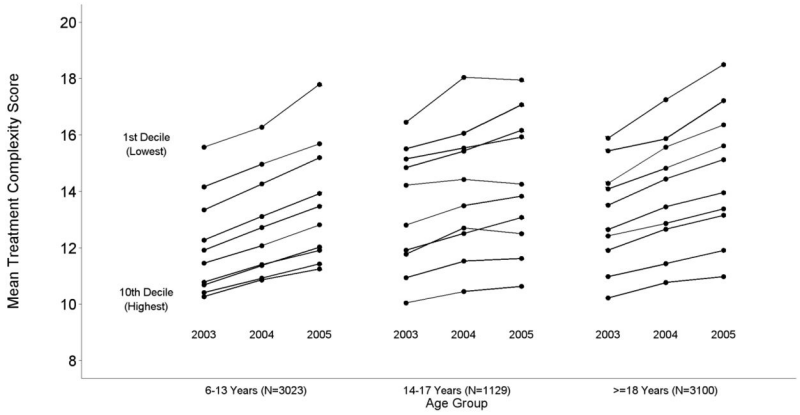

Figure 1. Mean Treatment Complexity Scores for Each Year by Age Group and Age-Adjusted FEV1 Percent Predicted Decile*

* The test for trend for each decile in each age group is statistically significant ($P < 0.05$) except for decile 5 for age 14-<18 ($P=0.89$). The statistical significance of differences between deciles varies somewhat by age group. For age groups 6–13 years and 18 years, differences of 1.16 points or more are always significant ($P < 0.05$) and many differences as small as 0.5 points are significant. For Age group 14–17 years, most differences of 1.7 points or more are significant, but differences involving Decile 1 may need to be as large as 2.5 points to be significant.

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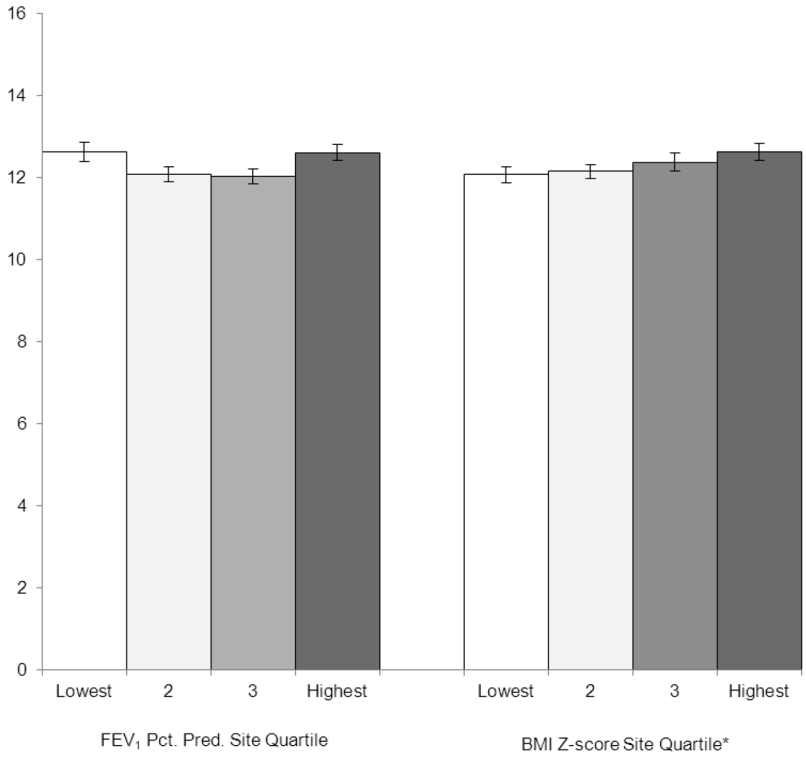

Figure 2. Treatment Complexity Scores by Site-specific Quartiles for FEV_1 Percent Predicted and BMI Z-score

*p<0.001 for differences between highest and lowest site quartile and for trend over quartiles for BMI z-score.

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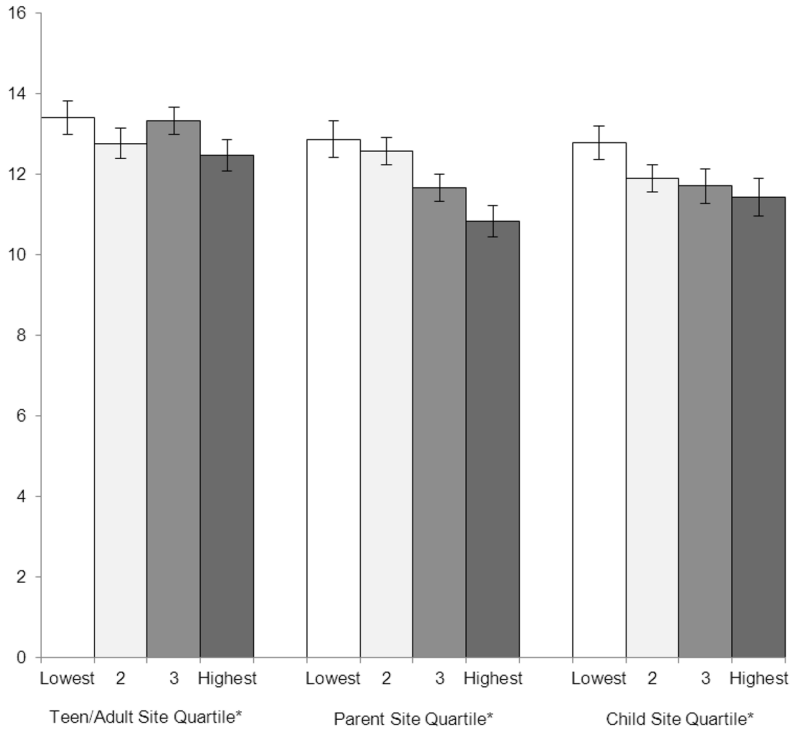

Figure 3. Treatment Complexity Scores by site-specific quartiles for CFQ-R Treatment Burden Score

*p<0.001 for differences between highest and lowest site quartiles and for trend over quartiles.

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Table 1

Definition of Treatment Complexity Score

TCS Score = 1 point	TCS Score = 2 points	TCS Score = 3 points
Inhaled bronchodilator	Hypertonic saline	Airway clearance technique
Oral bronchodilator	N-Acetyl cysteine (Mucomyst)	CPAP/BIPAP
Inhaled corticosteroid	Pancreatic enzymes	Oxygen
Oral corticosteroid	Inhaled TOBI (once per day)	Enteral supplement
High dose ibuprofen	Inhaled other aminoglycoside (once per day)	Parenteral supplement
Leukotriene inhibitor/antagonist	Inhaled Colistin (once per day)	Inhaled TOBI (twice daily)
Cromolyn/mast cell stabilizer	Other inhaled chronic suppressive antibiotic	Inhaled other aminoglycoside (twice daily)
Gastric acid suppressors	Dornase alfa	Inhaled Colistin (twice daily)
Oral supplement		Insulin
Ursodiol		
Vitamins		
Oral Quinolone		
Oral Azithromycin (thrice weekly)		
Other Oral Antibiotics		
Antidepressants		
Anxiolytics		
Contraceptive/hormonal methods		
Oral hypoglycemic		
Pain medications (chronic)		
Diuretic		

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Table 2

Patient Characteristics for TCS Trends Over Time Analysis

N	**7252**
Characteristic	**Percentage**
Age	
6–13	41.7%
14–17	15.6%
≥18	42.7%
Male	52.3%
Genotype	
Homozygous dF508	42.8%
Heterozygous dF508	32.1%
Other	8.8%
Unknown	16.4%
Non-Hispanic White	90.7%
FEV_1	
<40% predicted	8.4%
40%–<70% predicted	23.3%
70%–<100% predicted	41.0%
≥100% predicted	27.2%
Age-adjusted FEV_1 Decile	
1st Decile (Lowest)	2.0%
2nd Decile	3.6%
3rd Decile	4.7%
4th Decile	6.0%
5th Decile	7.3%
6th Decile	9.7%
7th Decile	11.2%
8th Decile	13.8%
9th Decile	17.3%
10th Decile (Highest)	24.5%

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Table 3

Site-specific quartiles for FEV_1 Percent Predicted, BMI Z-score, and Treatment Burden scores (2004 data)

Quartile	FEV_1 Pct. Pred.		BMI Z-score		Treatment Burden (Teen/Adult)		Treatment Burden (Parent)		Treatment Burden (Child)	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Highest Quartile	3467	89.9	3241	−0.05	699	68.4	334	72.9	231	77.0
3rd Quartile	3328	83.6	2891	−0.27	742	63.6	499	65.8	334	72.2
2nd Quartile	3583	75.7	3872	−0.46	501	59.5	280	59.7	319	67.6
Lowest Quartile	2554	68.7	2833	−0.64	478	54.0	191	54.1	207	61.3

The quartile assessment was performed by age group within site, but is presented for all age groups combined.

Patients can be represented more than once if they switched age groups mid-year and met inclusion criteria for each age.

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Table 4

Demographic Comparisons between Lowest and Highest Quartile Sites for CFQ-R Treatment Burden Scores

Teen/Adult CFQ-R	**Lowest Quartile (N = 447)**	**Highest Quartile (N = 536)**	**P value***
Age, mean ± SD	26.1 ± 9.9	23.8 ± 9.0	<.001
FEV_1, mean ± SD	67.9 ± 24.2	71.9 ± 25.8	.013
Female, n (%)	211 (47.2)	244 (45.5)	.60
Non-Hispanic White, n (%)	413 (92.4)	511 (95.3)	.053
Medicaid, n (%)	152 (34.3)	174 (32.9)	.64

Parent CFQ-R	**Lowest Quartile (N = 249)**	**Highest Quartile (N = 327)**	**P value***
Age, mean ± SD	9.1 ± 2.0	9.2 ± 2.0	.51
FEV_1, mean ± SD	94.1 ± 19.7	98.3 ± 19.7	.012
Female, n (%)	120 (48.2)	172 (52.6)	.29
Non-Hispanic White, n (%)	232 (93.2)	295 (90.2)	.21
Medicaid, n (%)	164 (66.1)	140 (43.5)	<.001

Child CFQ-R	**Lowest Quartile (N = 252)**	**Highest Quartile (N = 254)**	**P value***
Age, mean ± SD	9.2 ± 2.0	9.3 ± 2.0	.49
FEV_1, mean ± SD	94.8 ± 19.1	100.3 ± 20.3	.002
Female, n (%)	116 (46.0)	134 (52.8)	.13
Non-Hispanic White, n (%)	198 (78.6)	233 (91.7)	<.001
Medicaid, n (%)	169 (67.3)	108 (42.5)	<.001

* P value obtained from chi square test statistic or student's t-test, as appropriate.