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High Treatment Burden in Adults with Cystic Fibrosis: Challenges to Disease Self-Management

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Abstract

Background—More aggressive management of cystic fibrosis (CF), along with the use of new therapies, has led to increasing survival. Thus, the recommended daily treatment regimens for most CF adults are complex and time consuming.

Methods—In the Project on Adult Care in CF (PAC-CF), an ongoing longitudinal study of CF adults, we assessed self-reported daily treatment activities and perceived treatment burden as measured by the CF Questionnaire-Revised (CFQ-R), a disease-specific quality of life measure.

Results—Among the 204 respondents, the median number of daily therapies reported was 7 (IQR 5-9) and the mean reported time spent on treatment activities was 108 minutes per day (SD 58 minutes). Respondents reported a median of 3 inhaled and 3 oral therapies on the day prior to the survey. Only 49% reported performing airway clearance (ACT) on that day. There were no differences in the number of medications or the time to complete therapies based on gender, age or FEV1. The mean CFQ-R treatment burden domain score was 52.3 (SD 22.1), with no significant differences in the treatment burden based on age or FEV1. In a multivariable model controlling for age, gender, and FEV1, using 2 or more nebulized medications and performing ACT for ≥30 minutes were significantly associated with increased treatment burden.

Conclusion—The level of daily treatment activity is high for CF adults regardless of age or disease severity. Increasing number of nebulized therapies and increased ACT time, but not gender, age, or pulmonary function, is associated with higher perceived treatment burden. Efforts to assess the effects of high treatment burden on outcomes such as quality of life are warranted.

Keywords

Cystic fibrosis; treatment burden; quality of life

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Introduction

The survival of patients with cystic fibrosis (CF) continues to increase, leading to a growing population of adults living with CF as a chronic illness. In 2005, over 40% of the US CF patient population was over the age of 18, and the median predicted survival for patients with CF has now reached over 36 years.[1] The dramatic increase in longevity in CF occurred not because of the development of a single therapy, but rather due to the development, widespread adoption and maintenance of a clinical care structure which supports patients in complex regimen of preventions and treatment. For most adult patients, CF care requires, at a minimum, the daily intake of pancreatic replacement enzymes, nutritional monitoring, airway clearance, inhaled and nebulized medications, oral anti-inflammatory medications, and quarterly visits to a specialist clinic.[2, 3]

Treatment advances in CF require increasing time and effort and pose continuous challenges to patient self-management strategies, particularly in adults trying to balance family, work, education, and other responsibilities with management of chronic disease.[4] Studies of treatment adherence in adults with CF suggest that levels of adherence to treatment regimes are similar to those in other chronic illnesses, though they vary by the type of treatment. Adherence to antibiotic treatment is highest (80-95%), nebulized medications and pancreatic enzymes is moderate (65-80%), and vitamin therapy, dietary changes, exercise, and physiotherapy is lowest (40-55%).[5] These levels of adherence suggest that adults with CF make daily decisions about which of the complex array of prescribed therapies they can complete while fulfilling their responsibilities and commitments to family and work. In an era of an increasing number of additive therapies in CF, understanding what therapies adults actually complete and what factors influence their choice of therapies on a daily basis has become increasingly important. Such understanding would provide the foundation for improvements in treatments, health outcomes, and quality of life of adults with CF as well as guide the development of interventions to support and enhance adherence.[5]

One factor that may influence treatment choices is perceived treatment burden. As the number of therapies increase, there may be a point at which perceived treatment burden outweighs the benefits of new or additive therapies, adversely affecting patient adherence. As a result, perceived treatment burden has been incorporated into CF-specific HRQOL scales and is measured as an important outcome in clinical trials.[6] For instance, in a large trial of nebulized hypertonic saline therapy, many aspects of HRQOL in CF did improve, yet perceived treatment burden was increased.[7] Shortening treatment time or improving drug delivery systems has also become a goal in the development of newer CF therapies, particularly inhaled antibiotics, with the intention of decreasing perceived treatment burden.[8] Substantial treatment burden has been demonstrated in children with CF, whose caregivers in one study reported spending 74 minutes per day on treatment tasks.[9] However, similar data for adults with CF has not been reported, and is likely to be higher given the natural progression of disease.

As a first step towards understanding decision-making about CF treatments, we assessed both treatment activities and perceived treatment burden among the cohort of adults with CF participating in the Project on Adult Care in CF (PAC-CF), an ongoing longitudinal study of quality of life in adults with CF. Our specific aims were to describe the daily treatment activities of CF adults and to examine the relationship between treatment activities and perceived treatment burden after controlling for disease severity in this population.

Methods

Study participants

The Project on Adult Care in Cystic Fibrosis (PAC-CF) is an ongoing prospective, longitudinal panel study of adults with CF. Adults 18 years of age or older receiving care at one of ten participating CF Centers were eligible for the study. The study design and recruitment for PAC-CF has been previously described.[10] Prior to enrollment, de-identified data from each center was used to calculate each individual's predicted probability of surviving 5 years, using Liou's rigorously developed prognostic model.[11] All adults with a predicted probability of 5-year survival less than 0.975 and a randomly selected 25% of adults with a predicted probability of 0.975 or higher were recruited for the study beginning in Fall 2004. This stratified sampling design was adopted because adults with a very high predicted probability of survival were least informative with respect to the overall PAC-CF goal of examining trends over time in quality of life as CF progresses. The results in this report come from the 6th survey wave of PAC-CF, administered to 294 participants in October 2006. The study protocol was approved by the Institutional Review Boards at Educational Development Center, Inc. and the ten hospitals in which the participating CF Centers are located.

Measures

Treatment activities were assessed through a series of survey questions in which we asked respondents to report the medications and therapies that they took on the day prior to the survey. In contrast to other self-report surveys which focus on self assessment of the degree of adherence to the regimen, we took an approach based on self management principles in asking adults to report which treatment activities they had engaged in yesterday, whether the activities were at a level more than or less than their usual activity, and why there had been a difference from their usual pattern. In addition to asking how many times during the day the treatment was taken or performed, we also included response options such as “the treatment is prescribed, and I usually do it, but I did not do it yesterday” and “the treatment is prescribed but I never do it.” We specifically prompted about 18 common CF medications (nebulized, oral, inhaled via a metered-dose inhaler (MDI), and other) and 6 common airway clearance techniques. In contrast to a self-report question on adherence in general, our questions allowed for responses that indicated that a respondent had made a decision about a therapy on a particular day as part of their overall disease self-management strategy.

Treatment burden was assessed using the treatment burden subscale of the adolescent and adult version of the Cystic Fibrosis Questionnaire (CFQ-R), a CF-specific measure of HRQOL.[12] The treatment burden subscale, which is comprised of 3 questions, is scored on a standardized 0- to 100-point scale on which lower scores represent higher treatment burden. The questions on the treatment burden scale in CFQ-R are the following: to what extent do your treatments make your daily life more difficult?, how much time do you currently spend each day on your treatments?, and how difficult is it for you to do your treatments each day?

Statistical Analysis

All analyses were performed with SAS software version 9.1 (SAS Institute, Cary, NC). Descriptive statistics, calculated using sample selection weights (the inverse of the probability of selection) to adjust for the disproportionate stratified sampling design, were used to summarize the demographic and clinical characteristics of the sample and to describe the prevalence and characteristics of treatment activities and treatment burden. Subgroup differences by respondent age, gender, and FEV_1 were assessed using weighted t-tests or ANOVA, as appropriate. Respondents were divided into four age groups: 18-24, 25-34, 35-44, and 45+ and three groups based on their best FEV_1 (% predicted) in 2005: less than 40%, 40-69%, and 70% and greater. Differences in CFQ-R treatment burden domain scores by level

of treatment activities were assessed using t-test or ANOVA. Multivariable linear regression was used to examine the association of treatment activities with the CFQ-R treatment burden score, after controlling for age, gender, and pulmonary function. Four types of treatment activities (nebulized medication, inhaled medication, oral medication, and airway clearance) were dichotomized into high and low levels of activity and included as predictors in the model. Stepwise procedures were used to identify independent predictors and the final multivariate model excluded nonsignificant predictors.

Results

Treatment Activities Reported by CF Adults

The treatment activity survey was completed by 204 / 294 PAC-CF participants (response rate 69%). The demographics and clinical characteristics of the respondents are shown in Table 1. Respondents reported taking many different types of medications on the day prior to the survey (Table 2). The median number of total medications reported was 7 (range 0-20). Respondents reported using the largest number of oral medications (median 3 per day) and nebulized medications (median 2 per day). When asked to approximate the number of minutes usually spent on CF therapies, respondents indicated a mean of 108 minutes per day on all therapies, with a mean of 41 minutes per day for nebulized therapy, and 29 minutes per day for airway clearance, and 29 minutes per day for exercise (Table 2). The reported time for treatments and the number of total medications reported did not differ significantly by patient age, FEV1, or gender.

Medications that were reported as taken on the day prior to the survey by a large number of respondents included pancreatic enzymes (85%), a beta-agonist (65%), anti-reflux medication (50%), DNase (49%), and azithromycin (47%). Fewer respondents reported taking inhaled steroids (36%), oral antibiotics (35%), nasal steroids (33%), hypertonic saline (30%), anti-histamines (29%), or inhaled tobramycin (29%). Some respondents reported that they normally take certain medications, but did not take them on the day prior to the survey. This was most commonly reported for azithromycin (22%), nasal steroids (13%), stool softeners (13%), beta-agonists (10%), and oral antibiotics (10%). Of the 190 respondents (93%) who reported using at least one inhaled or nebulized therapy, thirty-nine respondents (21%) said they were using more than usual therapy. The most commonly reported reasons for using more inhaled therapies than usual were feeling sicker (69%), and having enough time to complete therapies (22%). Only 18 (9%) said they were using less than usual therapy. The most common reasons reported for using less than usual therapy were forgetting (29%), being too busy (29%), preparing for another event (24%), and feeling healthier than usual (18%). Running out of a medication was only cited by a small minority (7%) of these respondents.

One hundred thirty-nine respondents (68%) reported performing at least one airway clearance technique (ACT). The most commonly reported ACT was the Vest (37% of all respondents), followed by autogenic drainage (25%), manual chest physical therapy (19%), and a flutter device (15%). Twenty percent of respondents reported that they normally use a flutter device, but did not use it the day prior to the survey. A similar response was given by 13% for the Vest and 13% for manual chest physical therapy. Seventeen percent of the respondents reported that they do not use a flutter device even though it is prescribed, and similar responses were seen for the Vest (11%) and manual chest physical therapy (9%). With regards to exercise, the majority of respondents (87%) reporting walking, with 29% reporting organized sports activities, 27% bicycling, 25% using weight training, and 20% jogging. Of the 65 respondents who did not report doing ACT, 42 (64%) reported that this was the same as usual. Among the 23 respondents who reported that no ACT during a day was less than usual, the most commonly cited reasons were feeling healthier (30%), being too busy (20%), getting ready for another event (17%), forgetting (10%), or using exercise as an alternative form of ACT (10%).

Treatment Burden in CF Adults is Associated with Treatment Activity

The mean CFQ-R treatment burden domain score for the cohort was 52.3 (SD 22.1). Females reported a higher treatment burden (mean score 49.9 vs. 56.5, p=0.04), but there were no significant differences in the treatment burden scale scores based on age or FEV1 (Table 3). Table 3 also shows the differences in CFQ-R treatment burden domain score based on different treatment activities reported. Reporting more treatment activities was uniformly associated with higher treatment burden (i.e. a lower CFQ-R treatment burden subscale score). Specifically, taking more types of nebulized, inhaled, and oral medications were all associated with higher treatment burden, as was reporting more times per day for taking medication and performing any airway clearance. In a multivariable model controlling for age, gender, and FEV1, using 2 or more nebulized medications and performing airway clearance for 30 or more minutes during the day were the treatment activities that remained significantly associated with a lower CFQ-R treatment burden score (Table 4).

Discussion

In this study of adults with CF cared for at 10 treatment centers throughout the United States, a high level of daily treatment activities was reported, with almost two hours per day being devoted to the completion of CF therapies. Perceived treatment burden, as measured by the CFQ-R, was not associated with disease severity as measured by pulmonary function, but was significantly higher in adults who reported completing 30 minutes or more of airway clearance and using 2 or more nebulized therapies. At a time when CF survival is increasing and new therapies are emerging, these results highlight the significant treatment demands already placed on adults with CF.

Treatment burden, both objective and perceived, in a chronic disease such as CF is a function of several factors, including the number of therapies required on a daily basis, the frequency of such therapies, the complexity of administering therapies, and the amount of time needed to complete a therapy. Perceived treatment burden also depends on how an individual views their treatment regimen within the context of their other daily demands and responsibilities such as family and work. A recent study showed that treatment burden is high in children with CF,[9] thus it is no surprise that we found a similarly high treatment burden in CF adults. Interestingly, we found no significant differences in the number of reported therapies or overall treatment burden based on age or FEV_1, confirming that high treatment burden in CF begins in late childhood, continues into adulthood, and is independent of disease severity. The observation that standard markers of disease severity such as FEV_1 are not associated with an individual's perceived treatment burden is not surprising since most maintenance CF therapies are initiated prior to adulthood, and often prior to disease progression. As such, the persistence of high treatment demands in adult CF care reflects the goals of CF chronic therapies, which in the absence of curative therapy, are designed to slow disease progression and extend survival.

A key finding in our analysis is that treatment activities, particularly the number of nebulized therapies and the time spent on airway clearance, and not disease severity, are independently associated with a higher treatment burden. This underscores the importance of evaluating perceived treatment burden as an outcome in the development of new CF therapies. Since many of these therapies are designed to be additive to the existing treatment regimen, treatment burden may continue to increase with their use. Indeed, treatment burden was the only quality of life measure which worsened in the recent randomized trial of hypertonic saline.[7] It is encouraging therefore that lowering treatment burden has become one stated goal in the development of new inhaled antibiotic therapies using novel delivery devices designed to reduce overall treatment time.[8]

Regular airway clearance has been recommended as a key component of daily CF therapy. In our survey, the majority of respondents did report performing some type of ACT or exercise. However, almost one-third of respondents did not report an ACT activity on the day prior to the survey, and two-thirds of this group stated that no ACT was usual for them. Thus, approximately 20% of our respondents report not performing any regular ACT. This is consistent with other studies of ACT in CF adults,[13] and underscores the need to understand the factors influencing patient choices with respect to ACT. CF clinicians, therefore, need to promote ACT adherence in the context of understanding the treatment burden that ACT imposes.

The CF Foundation recently issued guidelines for pulmonary maintenance medications based on a rigorous review of clinical trials, and strongly recommended the daily use of DNase and inhaled tobramycin, and recommended daily use of hypertonic saline and regular use of azithromycin.[2] The treatment burden of following these recommendations is clearly significant. Our findings on reported daily treatment activities suggest that many adults may be taking fewer maintenance therapies than are recommended on a given day. For instance, only one-half of our cohort reported the use of DNase on the day prior to completing their survey. Such treatment choices are likely occurring on a daily basis, perhaps in an effort to reduce treatment burden, and need to be better understood in the context of patient self-management. Particularly since perceived treatment burden may be impacting self-management, future study of challenges to successful self-management is needed. Such studies, including our ongoing work with the PAC-CF cohort, will need to focus on the relationship between symptom status, treatment burden, illness perceptions, and competing priorities on the daily treatment decisions made by adults with CF.

The focus on disease self-management is an important conceptual advance in the understanding of chronic illness and improving outcomes. Our survey questions signaled an expectation on our part that CF adults are making decision as to which treatments to do each day, and that there were acceptable reasons why adults might do so. These reasons need to be incorporated into a new view of CF disease self-management, one in which we gain a deeper appreciation of the active role adults can play in determining their treatment goals and integrating recommended behaviors into their lives. In fact, in our survey, adults were willing to admit not completing a recommended treatment. For example, one quarter of adults said they did not complete any airway clearance yesterday even though it was recommended. The main stated reasons for not completing usual therapies included being too busy and forgetting, both of which have been cited in prior studies on CF adherence.[14] Importantly, these reasons suggest that the high treatment burden created by the multitude of CF maintenance therapies is a major factor in day-to-day patient decision making.

Our survey has several limitations. We did not examine medical records so we cannot ascertain what treatment regimens were prescribed by their clinicians. However, our goal was not to assess adherence to prescribed regimens. We sought to describe treatment activities as reported by the patient as a step towards understanding patient-based disease self-management. Our treatment activity survey was designed to capture the daily choices that CF adults may make about their therapies rather than treatment adherence. Although we cannot completely eliminate the possibility of over-reporting treatment activity, by asking respondents to report the therapies that they actually used on the day prior to the survey, we strove to avoid such over-reporting by specifically wording the questions to avoid seeming critical about non-compliance. In addition, this study did not measure other factors which may influence treatment activity or perceived treatment burden such as illness perceptions and treatment beliefs.[15] Finally, since this is a cross-sectional survey, we also are unable to comment on how treatment burden changes with disease progression, additions or changes to therapy over time, or with

differences in patient treatment choices over time. The longitudinal data from the PAC-CF cohort will allow for such analyses in the future.

In summary, daily treatment activities and perceived treatment burden are high in all adults with CF regardless of age or disease severity. Increasing number of nebulized therapies and increased time spent on airway clearance, but not age or pulmonary function, is associated with higher perceived treatment burden. Given the high load of daily therapies, efforts to understand the determinants of and to lower treatment burden in CF are warranted. Ultimately, clinicians need the information, skills, and tools with which to assess both the actual and perceived treatment burden of their individual patients in order to help those patients cope with the daily demands of living with CF.

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Table 1

PAC-CF Respondent Demographics

Number of Respondents (n)	204
Female (%)	62%
Age (years) (Mean ± SD)	35.4 ± 10
FEV1 (% predicted) (Mean ± SD)	61 ± 20
Pancreatic Sufficient (%)	15%

Table 2

Treatment Activities Reported by CF Adults

	# Medications Reported Taking Yesterday	
	Median	**Range**
Total	7	0-20
Nebulized	2	0-5
Inhaled	1	0-4
Oral	3	0-7
	# of Minutes Needed to Complete Therapy	
	Mean	*SD*
Total	108	58
Nebulized	41	31
Oral	9	8
Airway Clearance	29	27
Exercise	29	23

Table 3

CFQ-R Treatment Burden Scale Scores Differ Based on Treatment Activities

	n	CFQ-R Treatment Burden Scale[c] Mean (SD)
Overall	204	52.3 (22.1)
Gender[a]		
Male	77	56.5 (23.0)
Female	127	49.9 (21.3)
Age (years)		
18-24	29	55.9 (17.6)
25-34	70	53.4 (21.8)
35-44	66	48.4 (20.7)
>45	38	55.1 (28.5)
FEV1 (% predicted)		
<40%	27	48.1 (20.2)
40%-70%	97	51.1 (20.4)
>70%	55	55.2 (24.1)
# Nebulized Medications[a]		
0	46	64.3 (24.0)
1	48	59.1 (16.0)
2	46	43.9 (20.6)
≥3	64	45.8 (20.7)
Performed ACT[a]		
No	62	62.8 (23.1)
Yes	142	47.4 (20.0)
# Inhaled (MDI) Medications[a]		
0	38	60.6 (21.9)
1	62	58.4 (20.2)
2	70	47.0 (20.7)
≥3	34	41.1 (21.6)
# MDI Times/Day[a]		
0	38	60.6 (21.9)
1-2	65	58.0 (20.8)
3-4	64	48.1 (20.2)
≥5	38	39.7 (21.1)
# Oral Medications[a,b]		
0-1	70	59.7 (24.8)
2-3	96	48.4 (19.3)
≥4	38	46.7 (20.0)
# Oral Medication Times/Day[a,b]		
0	28	65.9 (25.1)
1-2	62	53.8 (21.9)
3-4	74	46.6 (17.6)

	n	CFQ-R Treatment Burden Scale[c] Mean (SD)
≥5	41	48.8 (23.2)

[a] $p < 0.05$

[b] For oral medications, pancreatic enzymes were excluded from analysis

[c] CFQ-R Treatment Burden Scale is from 0-100, with a lower score representing a higher treatment burden

Table 4

Predictors of Higher Treatment Burden: Multivariate Linear Regression Results **

	Adjusted*	
Level of Activity	**Parameter**	**p**
≥2 nebulized medications	-9.61	.0024
≥2 inhaled medications		NS
≥3 oral medications		NS
≥30 minutes for ACT	-12.72	.0001

* Adjusted for age, gender, FEV1, adjusted R-squared = 0.198

** Using ≥2 inhaled medications and ≥3 oral medications were not significant predictors were dropped from the model during stepwise selection.