Efficacy of Problem-Solving Intervention to Improve Adherence in Adolescents and Adults with Cystic Fibrosis

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ABSTRACT

Background: Adherence to treatment by adolescents and adults with cystic fibrosis (CF) is often poor.

Objectives: To assess the impact of a focused clinical intervention on adherence in individual patients, including help in problem-solving key barriers to adherence. To implement a patient-centered problem-solving intervention using CF My Way tools. To identify and overcome a selected barrier to adherence.

Methods: Medication possession ratios (MPRs), number of airway clearance sessions, forced expiratory volume (FEV_1), body mass index (BMI), and health-related quality of life (HRQoL) were measured before and after the intervention.

Results: Sixteen patients with CF, aged 23.4 ± 6.7 years, participated. MPR increased for colistimethate sodium and tobramycin inhalations from a median of 21 (range 0–100) to 56 (range 0–100), $P = 0.04$ and 20 (range 0–100) to 33.3 (range 25–100), $P = 0.03$, respectively. BMI standard deviation score rose from -0.37 to -0.21, $P = 0.05$. No significant improvements were found in FEV_1, airway clearance, or HRQoL scores.

Conclusions: The CF My Way problem-solving intervention increased adherence to medical treatments by removing barriers directly related to the needs and goals of young adults with CF.

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KEY WORDS: adherence, adolescents, CF My Way, cystic fibrosis (CF), medical possession ratio (MPR)

Cystic fibrosis (CF) is the most common, life-shortening genetic disease in Caucasian populations, affecting approximately 31,000 individuals in the United States (CF Foundation, 2019). Treatment is highly complex and burdensome [1] including pancreatic enzyme replacement therapy, multiple oral medications, daily airway clearance, and inhalations. These treatments take 2 to 4 hours daily [2]. Thus, adherence is critical to improving medical outcomes. Recent U.S. data show that from ages 6 years through adulthood, adherence to all inhaled medications and airway clearance is 50% or less, with a significant drop during adolescence and emerging adulthood [3]. Thus, interventions to improve adherence in this age group are critically important.

Adolescents tend to feel invincible, while lacking knowledge about the health consequences of poor adherence. [4]. As teens transition toward independence and autonomy, they test rules and boundaries, and receive less parental supervision [5]. Brief behavioral interventions result in improved adherence in adolescents with other chronic conditions, such as diabetes and human immunodeficiency virus [6,7]. In CF, although effective in improving eating behaviors and nutrition in younger children [8], few interventions have been evaluated in adolescents and emerging adults. The CF My Way intervention utilizes a brief behavioral, problem-solving intervention (developed by A. Quittner) implemented in the clinic to target individual, personalized barriers that impede adherence. It emphasizes the patient's collaborative role in identifying barriers and generating solutions [9].

This study evaluated a 12-month clinical intervention utilizing the CF My Way problem-solving intervention. Key physical health outcomes, predicted forced expiratory volume (FEV1), and body mass index standard deviation score (BMI SDS), as well as frequency and duration of airway clearance sessions (by self-report), and health-related quality of life (HRQoL) were assessed.

PATIENTS AND METHODS

PARTICIPANTS

Patients aged 14 to 35 years, attending the Graub CF Center at Schneider Children's Medical Center, Israel, participated. Written consent to participate and to allow access to prescription refill data from pharmacies was obtained from those aged 18 years of age and older or from the parents of those younger. The study was approved by the Rabin Medical Center ethics committee (IRB 0290-10°). Inclusion criteria were an established CF diagnosis [10] and a requirement for chronic daily CF medication for CF. Patients with major developmental or cognitive disorders were excluded, as well as patients on the transplant list.

THE CF MY WAY INTERVENTION

The CF My Way adherence program, developed by Quittner [9], is a brief, behavioral evidence-based intervention to improve adherence. All documents were translated to Hebrew and Arabic, and validated and adapted to the CF population in Israel in terms of medications and airway clearance procedures used in Israel.

The intervention consists of three steps. First, the patient is asked using a checklist to self-report their adherence, that is, frequency and duration of prescribed treatments. The patient then chooses a particular treatment to work on. The patient completes a new checklist of self-reported adherence at the start of each of the four interventions, each time perhaps choosing a different area of treatment to work on. The second step is a brainstorming session between the patient, a family member, and a CF care provider to generate new solutions to the barrier identified in the first step. As the leader of the session, the patient proposes the first solution and writes it on a note, which is placed on the wall. The other two participants then do the same. This process is repeated three times, providing a total of nine potential solutions. In the third step, these solutions are voted on, in the same order. A + mark indicates it would be worth trying and a – mark indicates it is not worth trying. Only a solution that gets all three + votes is considered, and if multiple solutions obtain all + votes (usually 3–4 solutions), the patient selects the solution to try first. Implementation of this solution is categorized (e.g., who, what, when, where) to maximize success. The other solutions that received three + votes are kept for possible use in the future. The psychologist conducts a follow-up meeting one week later, after each of the four interventions, to review and support the patient's progress. This time span was considered to be a sufficient amount of time and intervention for an effective behavioral treatment. As a part of the CF My Way protocol, the patient also completes a knowledge questionnaire [11], which assesses CF knowledge under four different domains (lung, nutrition, general and treatment), since disease knowledge is an important factor that can contribute to better adherence. However, we did not use this information as an objective endpoint since the calculated statistical value would have been too low to enable significant analyses with the other domains.

STUDY DESIGN

This 1-year single center study included four problem-solving sessions conducted during routine ambulatory visits at a time of clinical stability. All participants also attended a pre-intervention baseline and post-intervention debriefing session, which involved completing questionnaires and a medical assessment. Intervention sessions followed a structured protocol administered by designated personnel who had completed a standardized training session in the CF My Way adherence program conducted by A. Quittner.

DEMOGRAPHIC INFORMATION

Date of birth, gender, pancreatic function, and occupation were noted. Outcome measures for efficacy included four domains:

- *Pharmacy refill data and medication possession ratio (primary outcome measure)*
  Computerized data were available from all dispensing pharmacies and used to calculate medication possession ratio (MPR). Each pharmacy was asked to provide comprehensive refill histories covering a 2-year period, from 12 months prior to study onset to 12 months after enrollment. The MPR captured the amount of medication possessed by the patients, relative to what they were prescribed, according to the CF clinic medical records. Pharmacy refill data were continually updated throughout the study. As described by others [12] MPR was calculated individually for each medication. Values were truncated to 100% and the MPRs for each medication were averaged across all medications to obtain a composite medication possession ratio. The following pulmonary medications were included in the composite adherence score: colistimethate sodium inhalations, tobramycin inhalations, dornase alpha, and oral azithromycin. In addition, ADEK fat soluble multivitamins and pancreatic enzyme replacements were included. Adherence to pancreatic enzymes was also reported separately for the seven patients who chose to work on this treatment as a central element of CF care. These medications were selected due to strong evidence of their efficacy in improving CF health [13].

- *Medical information (secondary outcome measures)*
  Height, weight, BMI, BMI SDS (according to U.S. Center for Disease Control and Prevention norms) [14] as well as FEV1% predicted, were recorded at baseline.

- *Cystic Fibrosis Questionnaire Revised (CFQ-R)*
  The CFQ-R Adolescent/Adult version is a self-report questionnaire for individuals with CF aged 14 years and older. It is considered the gold standard for reporting CF impact and was completed pre- and post-intervention. It is a 50-item health-related quality of life (HRQoL) instrument designed to measure the physical, emotional, and social impact of CF. The measure consists of 12 subscales: physical functioning, role functioning, vitality, emotional functioning, social functioning, body image, eating disturbances, treatment burden, perceptions of health, weight, respiratory symptoms, and digestion. Scores range from 0 to 100, with higher scores indicating better HRQoL. This instrument has well-established reliability and validity; a change of 4 points is the minimal important difference score [15].

- *Airway clearance measure*
  The airway clearance questionnaire is a self-report measure assessing frequency and duration of airway clearance sessions performed over the 12-month intervention. It was

completed to record technique used, average time per session, frequency of sessions per day and week, and whether performed alone or with a physiotherapist.

STATISTICAL ANALYSIS

Data were analyzed using the BMDP statistical analysis software package (BMDP, 1993 Chief Editor: W. J. Dixon, University of California Press, Los Angeles, USA). Descriptive statistics were used to characterize demographic and medical variables. Means and standard deviations (SD) were calculated for continuous variables and percentages were computed for categorical variables. Analysis of variance (ANOVA) with repeated measures was used to demonstrate changes pre- to post-intervention. For those variables that did not have Gaussian distributions, we used the Wilcoxon signed rank test. A P value of ≤ 0.05 was considered significant.

RESULTS

Twenty-eight patients were eligible to participate, 9 declined and 19 (9 male, 10 female) were enrolled. Three did not complete the year-long intervention: 1 died and 2 did not complete the second intervention because of irregular clinic attendance. Sixteen patients, aged 23.4 ± 6.7 years, completed the entire year of the program, with 15 Hebrew speakers and 1 Arabic speaker. Demographic and clinical variables for these 16 participants are presented in Table 1.

There was a significant improvement in MPR for colistimethate sodium and tobramycin inhalation (TOBI) [Table 2]. For the colistimethate sodium no significant changes in MPR were found for the other treatments. Significant improvement was observed in the BMI SDS [Table 3] but not for FEV1% predicted or on any scales of the CFQ-R (using the Wilcoxon signed rank test). As shown in Table 3, frequency of airway clearance treatments increased for sessions performed alone but decreased for sessions performed with a physiotherapist. There was no change in the session duration.

BARRIERS CHOSEN FOR PROBLEM SOLVING INTERVENTION

During the 12-month intervention period, a total of 64 problem solving sessions were performed for the 16 patients as illustrated in Figure 1. Three predominant barriers were tackled in the problem solving sessions: exercise (33%), food intake (17%), and inhalation therapy (14%). The three patients who dropped out had a total of five interventions between them. The barriers addressed were exercise (60%) and airway clearance sessions (40%). It was not possible to analyze each intervention separately due to the small sample size. However, for the seven patients who chose to focus on food intake (diet), there was a significant increase in MPR for pancreatic enzyme replacement from 54.6% (11.3%–100%) to 72.8% (18.5%–100%), $P = 0.03$ (Wilcoxon signed rank test). For those who focused on exercise or inhalation therapy, no significant differences were found in any of the outcome measures.

INTERVENTION CASE ANALYSIS

Patient A chose to focus on airway clearance sessions for two of

Table 1. Demographic and clinical variables at baseline (n=16)

		n (%)
Age (years)*		23.4 ± 6.67
Female (%)		9 (56.3%)
Occupation	Employed	2 (12.5 %)
	Student	6 (31.3%)
	Military service	5 (37.5%)
	Unemployed	3 (18.7 %)
Ethnic group	Jewish	15
	Arab	1
FEV1 % predicted		73 ± 21
BMI SDS		-0.37 ± 0.54*
Pancreatic Insufficiency		12 (75%)

*mean ± SD
BMI SDS = body mass index standard deviation score, FEV1 = forced expiratory volume in 1 second

Table 2. Medication possession ratio before and after intervention

Medications	Medication possession ratio %		P value*
	Pre-intervention median (range)	Post-intervention median (range)	
Colistimethate sodium inhalation	21.0 (0–100)	56.0 (0–100)**	0.04
Tobramycin (TOBI) inhalation	20.0 (0–100)	33.3 (25–100)	0.03
Dornase alpha inhalation	55.6 (18.1–100)	41.7 (25–100)	0.25
Pancreatic enzyme replacement	57.5 (11.3–100)	70.5 (16.2–100)	0.11
ADEK multivitamins	20.5 (0–83.3)	20.5 (9.1–100)	0.26

*analyzed by Wilcoxon signed ranks test, n=16
**The range was 0–100, since one patient was at the zero range at the beginning of the intervention but then improved significantly after the intervention and another patient remained at zero after the intervention

Table 3. Pre-post changes in BMI, lung function, airway clearance frequency

	Pre-intervention mean ± SD	Post-intervention mean ± SD	P value*
BMI			
BMI SDS	-0.37 ± 0.54	-0.21 ± 0.54	0.05*
Lung function			
FEV1% predicted	73 ± 21	73 ± 25	0.72
Airway clearance frequency			
Times per day	0.8 ± 0.4	1.0 ± 0.4	0.03
Times per week: alone	0.9 ± 1.4	1.9 ± 1.9	0.03
Times per week: with physiotherapist	4.8 ± 2.2	3.8 ± 2.5	0.05
AC duration (minutes)	54.4 ± 11.7	48.8 ± 16.6	0.18

*Analysis of variance with repeated measures, n=16
AC = airway clearance, BMI SDS = body mass index standard deviation score, FEV1 = forced expiratory volume in one second

four PS sessions across the year and ascribed his poor adherence to lack of importance for him. However, after discussing the potential benefits of airway clearance, the chosen solution was to schedule a daily time (early evening). Frequency and duration of airway clearance sessions increased from zero to once a day, with a physiotherapist three times a week and independently on the other days. Overall airway clearance time performed alone increased by 10 minutes. Two of 3 of the subscales on the CFQ-R were relevant to airway clearance improved. Significant pre–post differences were found on the Health Perceptions (baseline score 25, post-score 58.3) and Vitality scale (baseline score 66.7, post-score 79.2). No significant differences were found on the respiratory symptoms score (baseline 83.3, post-score 79.2).

DISCUSSION

This study evaluated the efficacy of an adherence intervention that combined evidence-based psycho-educational and behavioral approaches in patients with CF [16]. The program is brief and cost-effective and can be implemented during a routine CF clinic visit [9]. This problem-solving model differs from other adherence programs in several important ways. First, it allows the individual with CF to lead the session, empowering the patient and potentially enhancing motivation and sense of control, which is critically important during this transitional period with a shift toward greater independence. This intervention method could benefit young patients with other chronic diseases and an overwhelming burden of care.
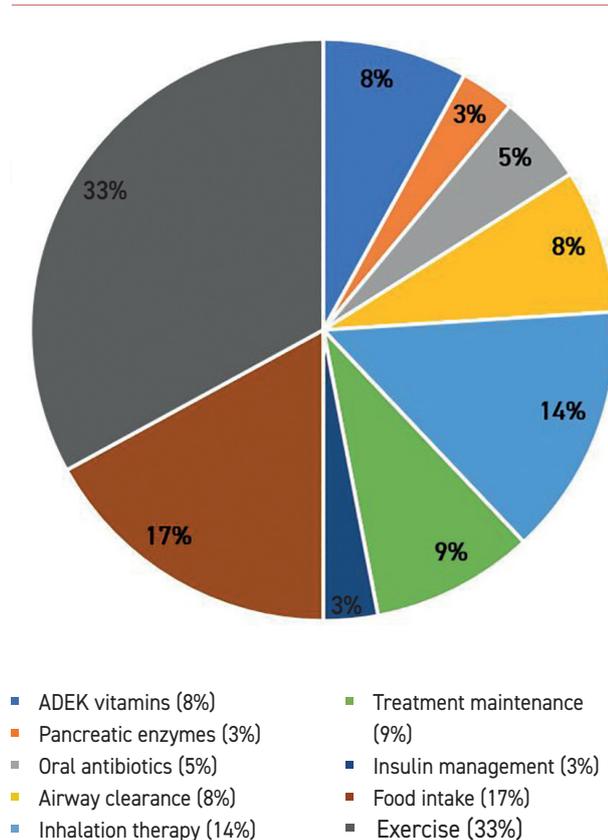
Second, the intervention is personalized, encouraging the patients to choose solutions that reflect and fit their lifestyle and val-

ues. It emphasizes an individualized, not one-size-fits-all approach, which has been shown to be effective in recent research [17]. Thus, problem solving addresses the importance of balancing treatment burden and health-related quality of life, using a non-judgmental approach. Third, it allows the CF team and other family members to participate in problem-solving adherence challenges and fosters open communication. Research has shown this approach to be valuable in reducing conflict and improving adherence [18].

It is surprising that there are so few published studies evaluating the effects of an individualized, behavioral intervention on medication adherence in CF. Indeed, Cochrane reviews have demonstrated that behavioral interventions are effective in improving medication adherence [19]. Clinic-based problem-solving has been shown to be effective with adolescents with diabetes and human immunodeficiency virus [6,7]. However, there is still a paucity of research on effective adherence interventions in CF.

The significant improvement in refilling inhaled medications is an important finding as documented by an increase in MPR. This feasible and relatively reliable yet indirect method for evaluating medication adherence [20] is more accurate than self-report, correlates with other measures of adherence, and predicts

Figure 1. Barriers chosen for intervention
n=16
% refers to % of all interventions selected of a total of 64 barriers

- ADEK vitamins (8%)
- Pancreatic enzymes (3%)
- Oral antibiotics (5%)
- Airway clearance (8%)
- Inhalation therapy (14%)
- Treatment maintenance (9%)
- Insulin management (3%)
- Food intake (17%)
- Exercise (33%)

pulmonary exacerbations to provide evidence for convergent validity. In addition, MPR ratios may be a useful basis for sensitive discussion about adherence between CF team and patients.

The significant increase documented in BMI for adolescents and young adults is noteworthy, as it occurred over the relatively short period of one year. This finding supports studies showing behavioral interventions to be effective regarding nutritional issues and boosting caloric intake in young children [8]. Although lung function did not improve, stability could be viewed favorably since lung function in CF declines by an average of 1–3% per year [21].

The lack of improvement in airway clearance or health related quality of life may have been due to this study being underpowered to show these differences. It is interesting to observe that frequency of airway clearance treatments increased for sessions performed alone. We speculate that empowering the patient to choose the intervention to work on may have improved the patient's feeling of self-efficacy and autonomy, which may have motivated the patients to take charge more of their own illness and hence do more individual airway clearance sessions. Indeed, it is of interest that exercise was the most popular barrier to treatment chosen and suggests a preference for common activities rather than specific CF medications. Nevertheless, exercise is a key component of the CF regimen and has been shown to lead to improvements in weight, physical endurance, and pulmonary function and also appears to lead to well-being, self-efficacy, and self-esteem [22]. As the first intervention chosen, this may be an important way to encourage adherence to other aspects of the regimen. Placing the locus of control with the patient has been shown to lead to more positive adjustment and disease management [23]. An additional point to mention is the encouraging effect of the phone call each week after each intervention. Although not possible to demonstrate quantitatively, CF patients reported feeling valued and motivated. The importance of telemedicine to improve adherence in adolescents must be highlighted [24] and needs to be considered in future research with adolescents and for CF adherence [25].

LIMITATIONS

The small sample size, compounded by patient's choice to work on different treatments, precluded the possibility of evaluating the effects of individual interventions. There was no control group but rather a within-subjects, pre–post design. Pharmacy refill records provide objective estimates of how often medications are picked up, but do not confirm ingestion or appropriate patterns of use [11]. However, this limitation applied in both the pre- and post-intervention assessments. Another limitation was that patients excluded from analysis due to poor clinic attendance were likely to also have poor adherence, which we could not evaluate in this study. With regards to airway clearance, we used a self-report measure, which has limitation including social desirability responding and inaccurate recall. Despite the more descriptive nature of these effects, significant improvements were observed following implementation of this intervention.

CONCLUSIONS

To the best of our knowledge, the present study is the first to show that a problem-solving intervention can increase rates of adherence as measured by MPR in adolescents and young adults with CF. A larger, randomized controlled trial is needed to verify these effects.

CONFLICT OF INTEREST (FUNDING)

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Capsule

Hitching a ride with a retroelement

Retroviruses and retroelements have inserted their genetic code into mammalian genomes throughout evolution. Although many of these integrated virus-like sequences pose a threat to genomic integrity, some have been retooled by mammalian cells to perform essential roles in development. **Segel** and colleagues found that one of these retroviral-like proteins, PEG10, directly binds to and secretes its own mRNA in extracellular virus-like capsids. These virus-like particles were then pseudotyped with fusogens to deliver functional mRNA cargos to mammalian cells. This potentially provides an endogenous vector for RNA-based gene therapy.

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Eitan Israeli

Capsule

Targeting the main protease of SARS-CoV-2

Inside host cells, the RNA genome of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is translated into two polyproteins that are cleaved to yield the individual viral proteins. The main viral protease, known as Mpro or 3CLpro, plays a key role in these cleavages, making it an important drug target. **Drayman** and co-authors identified eight drugs that target 3CLpro from a library of 1900 clinically safe drugs. Because of the challenge of working with SARS-CoV-2, they started by screening for drugs that inhibit the replication of a human coronavirus that causes the common cold. They then evaluated the top hits for inhibiting SARS-CoV-2 replication and for inhibiting 3CLpro. Masitinib, a broad antiviral, inhibited the main proteases of coronaviruses and picornaviruses and was effective in reducing SARS-CoV-2 replication in mice.

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Eitan Israeli

Capsule

Poultry passport to pandemic

What conditions are required to nurture the seeds of a pandemic? The avian influenza virus H7N9 rarely spills over into humans, but when it does, mortality exceeds 30%, far in excess of that of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). **Chen** et al. used whole-genome sequencing to investigate the contribution of rare mutations among poultry workers, who can be exposed to high levels of H7N9. Multiple defective single-nucleotide variants in the myxovirus resistance Mx1 locus were prevalent in H7N9 patients. In vitro infection experiments and influenza polymerase activity assays showed that 14 of the 17 MxA protein variants had no antiviral activity. Thus, when exposed to high virus loads, individuals with such genetic vulnerabilities may act as crucibles for transmission of virulent new influenza subtypes.

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Eitan Israeli