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Adherence to Nutritional Supplementation in Cystic Fibrosis

Kevin A. Hommel, Ph.D. [a,b,c,*], Joseph Rausch, Ph.D. [d,e], Elizabeth K. Towner, Ph.D. [f], Joan Schall, Ph.D. [g], Asim Maqbool, M.D. [g,h], Maria Mascarenhas, MBBS [g,h], Virginia Stallings, M.D. [g,h]

[a] Center for Adherence and Self-Management, OH, United States of America
[b] Cincinnati Children's Hospital Medical Center, OH, United States of America
[c] University of Cincinnati College of Medicine, OH, United States of America
[d] Nationwide Children's Hospital, OH, United States of America
[e] Ohio State University, OH, United States of America
[f] Wayne State University School of Medicine, MI, United States of America
[g] Children's Hospital of Philadelphia, PA, United States of America
[h] University of Pennsylvania Perelman School of Medicine, PA, United States of America

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ABSTRACT

Purpose: The purpose of this study was to examine patterns of adherence to a novel dietary supplement in pediatric cystic fibrosis. Adherence to dietary supplementation in cystic fibrosis is challenging, and examination of patterns of adherence behavior over time is needed to better characterize subgroups of patients who need self-management support.

Design and methods: We prospectively examined adherence to Lym-X-Sorb™ (LXS), an organized lipid matrix dietary supplementation for patients with cystic fibrosis (CF) and pancreatic insufficiency (PI), over a 12-month period. Adherence for participants aged 5–17 years with CF and PI (N = 109) was monitored monthly via supplement packet counts. Group-based trajectory modeling was employed to examine patterns in adherence behavior over time.

Results: Four distinct trajectories best characterized adherence in this sample, with 18% of participants demonstrating near perfect adherence, 42% demonstrating good adherence (at or above 80%), 16% demonstrating poor adherence that declined over time, and 24% demonstrating significant non-adherence (< 30%).

Conclusions: Some patients with CF and PI who are prescribed nutritional supplements will require intensive, individualized behavioral intervention to enhance adherence. Identifying patients who will have difficulty adhering to dietary interventions may result in better treatment-to-patient matching and improved adherence promotion efforts.

Practice Implications.

Assessment of adherence to dietary supplementation over time can identify patients at risk for continued difficulty with self-management and provide opportunities for early intervention.

Introduction

Cystic Fibrosis (CF) is a chronic and progressive condition caused by mutations in the CF transmembrane conductance regulator (CFTR) gene (Cutting & Zeitlin, 2012) and is characterized by lung infections and morbidities in other organs including the pancreas, resulting in pancreatic insufficiency. Due to advances in medical care in recent decades, survival rates have improved substantially and CF is no longer considered exclusively a pediatric condition, with half of the CF population consisting of adults (Jain & Goss, 2014). Nevertheless, with the diagnosis occurring during childhood and the importance of consistent treatment over time to maximize health outcomes, quality of life, and survival, the pediatric care context is a critical one for patients with CF and their families. CF is one of the most challenging chronic pediatric conditions with regard to treatment adherence. The complexity of treatment (i.e., number of medications or other treatments, differing modes of administration/types of treatments, timing, and burden of treatment) as well as shared responsibility for treatment between patients and their parents/caregivers contributes to low adherence observed in this population (A.L. Quittner et al., 2014); (A. L. Quittner et al., 2000). Indeed, non-adherence, typically operationalized as performing <80% of treatments, in CF varies across treatments, but has been reported at 52% for nebulized medication (Wilkinson & Paton, 1999), 51% for chest physiotherapy (Eddy et al., 1998), and 50% or less for all pulmonary medications (A.L. Quittner et al., 2014) and is significantly related to

* Corresponding author at: Center for Adherence and Self-Management, Division of Behavioral Medicine and Clinical Psychology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue MLC-7039, Cincinnati, OH 45229, USA.
E-mail address: kevin.hommel@cchmc.org (K.A. Hommel).

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pulmonary exacerbations (Eakin, Bilderback, Boyle, Mogayzel, & Riekert, 2011).

A particularly challenging aspect of treatment for CF is nutritional supplementation (Filigno et al., 2012; Janicke, Mitchell, Quittner, Piazza-Waggoner, & Stark, 2008; Powers et al., 2002; L. Stark et al., 1997; L. J. Stark, Bowen, Tyc, Evans, & Passero, 1990; L. J. Stark et al., 2000; L. J. Stark et al., 2003; L.J. Stark et al., 2009). Patients must take oral pancreatic enzyme replacement medication with each meal/snack to treat pancreatic insufficiency (PI). Moreover, due to the malabsorption associated with CF and PI, patients need to consume 110% or greater of the recommended daily intake (RDI) of calories to maintain adequate nutritional status and growth (Stallings et al., 2008). This is especially difficult for children as only 15% to 23% meet the increased energy needs for children with CF and PI (Anthony, Paxton, Bines, & Phelan, 1999; L. J. Stark et al., 1995; Tomezsko, Stallings, & Scanlin, 1992). As a result of the difficulty in consistently consuming sufficient food to meet the energy requirements for CF, nutritional supplementation may be used to increase intake and support better growth and pulmonary outcomes.

Lym-X-Sorb™ (LXS), an organized lipid matrix, was shown in a previous study to improve essential fatty acid (EFA), vitamin E and retinal binding protein status over a 12 month period and to improve both growth and pulmonary function over 18 months in subjects with CF and PI (Lepage et al., 2002). The second generation of LXS was developed to improve palatability and mixing characteristics and is provided in the form of a powder that is mixed with routinely consumed and preferred foods and beverages. This product was tested in a randomized controlled trial (RCT) to evaluate its effect on choline and EFA status as well as growth, nutritional and pulmonary function status, with subjects recruited from multiple sites in the eastern United States (Groleau et al., 2014).

Given the potential benefits of this dietary supplement, the aim of this study was to characterize participant use by determining LXS adherence trajectories over the course of a 12-month study using data from the Groleau et al., 2014 RCT. This is the first such study examining adherence to LXS. Adherence was assessed monthly via an objective measurement process. It was hypothesized that distinct adherence trajectories would be identified to best characterize participant adherence behavior.

Patients and methods

Participants and procedure

Patients with CF and PI who had mild to moderate lung disease and were 5.0 to 17.9 years of age were identified via medical chart review and recruited from ten CF Centers to participate in a placebo controlled double blind RCT. Exclusion criteria were FEV1 < 40% predicted, residual pancreatic lipase activity (fecal elastase >15 μg/g stool), liver disease (serum GGT >3× age-based reference range) or another chronic condition that affects growth or nutrient absorption. A total of 109 participants were randomized to either LXS or placebo supplementation for 12 months. Participants consumed two packets/day (64 g powder) for 5.0 to 11.9 year-olds, and three packets/day (96 g powder) for 12.0 to 17.9 year-olds. LXS is a composition of lysophosphatidylcholine (LPC), triglycerides and fatty acids that creates a choline rich lipid matrix mixed with flour and sugar. The placebo was similar with regard to calories, total fat, and macronutrient distribution (protein 6%, carbohydrate 58%, lipid 34% of kcal), and only 10% as much choline as LXS. Both LXS and the placebo supplement were identical in calories (157 kcal/packet), texture, and taste (Groleau et al., 2014). The Institutional Review Board at the Children's Hospital of Philadelphia (CHOP) and in each participating CF Center approved this protocol. Assent was obtained verbally from all participants and parents or legal guardians provided written informed consent. All study visits were at CHOP. Additional details regarding the overall study methodology are described in Groleau et al. (Groleau et al., 2014).

As part of the study, a supply of supplement was shipped to participants every 28 days. Each packet contained a number corresponding to the 28-day cycle of the study (e.g., first 28 days packet supply had the number "1" on the packet label, second 28 days packet supply had the number "2" on the packet label, etc.).

Demographic and physiological parameters

Participant demographic data including age, ethnicity, race, sex, annual income, and insurance status (private vs. public) were collected by participants via self-report and medical chart review. Insurance status is used as a proxy socioeconomic status measure as individuals in the United States who are on public health insurance generally do not have the economic resources that those with private insurance have. Physiological parameters including Z scores for height, weight and BMI, FEV1, and Tanner stage of pubertal development were collected.

Adherence assessment

Supplement adherence was measured via packet counts (analogous to pill counts) conducted during regular monthly telephone follow-up appointments with participants. Parents/caregivers of pediatric participants counted the remaining packets with the previous cycle number and reported that number to study staff. This number was subtracted from the number of packets provided for the 28-day period to arrive at the number of packets used and an adherence percentage was calculated (e.g., 8 packets remained: 56–8 = 48 ÷ 56 = 86%).

Statistical analyses

Longitudinal adherence data were described using group-based trajectory modeling (GBTM) (Nagin, 2005). GBTM is an appropriate analytic approach when interest lies in identifying and characterizing differential patterns of individual participant change over time. When using GBTM, individual participants are assumed to belong to only one group, and each group has its own unique trajectory for the outcome of interest over time. GBTMs assume that everyone classified within a given group follows the trajectory over time specified by the model.

In determining the most appropriate number of groups for adherence trajectories, one- to seven-group solutions were investigated based on cubic polynomial trajectories and a censored normal probability distribution for the average adherence percentage to identify the number of groups that characterizes the data most accurately. A cubic polynomial was used to allow for the possibility of non-linear trajectories over time when best characterizing the adherence trajectories for each group. A censored normal probability distribution was used due to the fact that our adherence was bounded by a minimum of 0 and a maximum of 100. Selection of the final model was based on the Bayesian Information Criterion (BIC; where the value closest to zero indicates the best fitting model), sufficiently large estimated trajectory group proportions (i.e., > 0.10), and the stability and interpretation of the extracted trajectories (Nagin, 2005). Adherence groups were also compared on demographic and relevant baseline variables using a chi-squared test for categorical variables or an analysis of variance for quantitative variables, ($p < .05$). SAS v9.3© and the PROC TRAJ Macro, a closed source module developed for use with SAS (http://www.andrew.cmu.edu/user/bjones) was used to estimate the GBTM.

Results

Table 1 presents demographics and other relevant baseline variables for the sample overall and for each GBTM group. No significant differences were observed between the LXS and placebo arms (thus, both arms were combined for adherence trajectory analysis). This was

Table 1
Descriptive statistics for demographic and physiological parameters in each adherence trajectory group.

Variable	Overall N = 109	Group 1 N = 26	Group 2 N = 17	Group 3 N = 46	Group 4 N = 20
Age (yr)	10.4 (3.0)	11.1 (3.2)	11.2 (2.8)	10.1 (3.2)	9.8 (2.4)
Sex (% Male)	57	42	73	60	56
Race (% White)	89	88	93	94	72
Ethnicity (% Non-Hispanic)	92	88	87	96	89
% On Medicaid*	27	46	13	18	33
Income ($1000/yr)	105 (56)	93 (55)	95 (39)	114 (59)	103 (64)
Height z-score	−0.40 (0.91)	−0.17 (0.94)	−0.66 (0.90)	−0.30 (0.87)	−0.82 (0.91)
Weight z-score	−0.39 (0.78)	−0.25 (0.91)	−0.60 (0.95)	−0.34 (0.69)	−0.56 (0.69)
BMI z-score	−0.20 (0.78)	−0.21 (0.87)	−0.23 (0.72)	−0.23 (0.82)	−0.09 (0.60)
FEV1, % pred.	95 (23)	94 (26)	96 (19)	96 (21)	94 (29)
Tanner Stage (breast/genital)	1.9 (1.2)	2.3 (1.5)	2.1 (1.2)	1.7 (1.0)	1.8 (1.0)
Tanner Stage (pubertal hair)	1.8 (1.3)	2.3 (1.4)	2.0 (1.4)	1.6 (1.3)	1.4 (0.9)

* $p = .03$ for chi-square test of group differences. % or Mean (SD) are presented. Group 4 = near perfect adherence; Group 3 = good adherence (at or above 80%); Group 2 = poor adherence that declined over the trial; Group 1 = consistently low adherence.

confirmed as similar trajectory solutions were obtained when estimating trajectories for each group separately. Furthermore, when examining treatment group differences on the trajectory solution obtained for the entire sample, no significant differences in treatment group were observed for the proportions for each trajectory type ($\chi^2(3) = 2.86$, $p = .41$). Chi-square analysis revealed a significant difference in adherence trajectories based on insurance status, with the most adherent and least adherent groups more likely to receive Medicaid than the middle two adherence groups. Our model (see Fig. 1) illustrates that, in general, there were substantially different (a) starting points for adherence and (b) amount of longitudinal change in adherence across the four groups that characterized adherence in this GBTM. Approximately 60% of the participants adhered well, with 18% (Group 4) demonstrating near perfect adherence and an additional 42% (Group 3) demonstrating good adherence (at or above 80%). In contrast, around 40% of participants exhibited moderate to significantly low adherence over time: 16% (Group 2) of participants demonstrated poor adherence that declined over the trial, and 24% (Group 1) demonstrated consistently low adherence (< 30%) for the duration of the trial. All groups demonstrated an increase in adherence initially, but around two to three months, this increase either plateaued or began to decline.

Discussion

The challenges of adhering to the multicomponent treatment recommendations for CF necessitate understanding of patient adherence to each component. As nutrition-related regimens are crucial to health in CF, yet pose unique adherence challenges, better understanding of patterns of supplement use is important. In this study four distinct trajectories of adherence were identified over a 12-month period, with

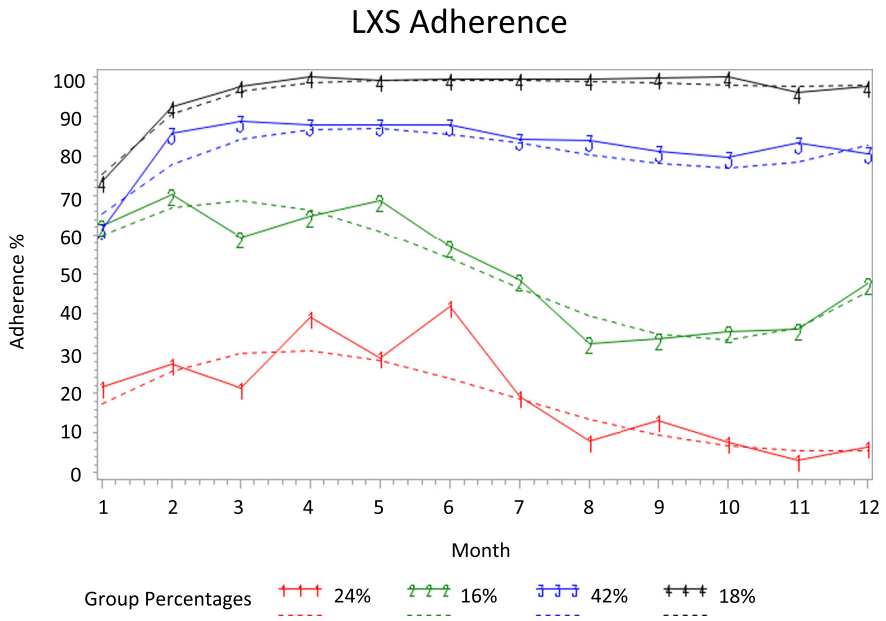

Fig. 1. Group-based adherence trajectory model Note: Solid lines represent the means at each time point; dotted lines represent the trajectories implied by the final model.

over half of the sample demonstrating adequate adherence and over a third demonstrating poor adherence. Although the treatment for which adherence was examined in this study is novel, these findings are fairly consistent with recent reports of dietary adherence in CF. For example, Simon and colleagues (Simon et al., 2011) found that 24% of children in their study were non-adherent to caloric intake goals, and 41% did not achieve the minimum recommendation of fat intake. Faulkner and colleagues (Faulkner, Taper, & Scott, 2012) found slightly better adherence to taking enzymes with meals (67%) and snacks (56%); however, the sample size (N = 9) was quite small. Both of these studies relied on participant recall/self-report of adherence in contrast to the current study, which utilized objective measurement of adherence.

As with any new treatment, unique adherence challenges may emerge. With LXS, the challenge for most participants may have been masking the texture/taste of the supplement across a variety of preferred foods and beverages, based on anecdotal reports from participants in this study. Recipes were given to parents of participants, and these were updated throughout the trial.

The fact that approximately 40% of the sample maintained trajectories of moderate to significantly low adherence suggests that some patients will require intensive intervention. Identifying patients who are likely to have poor adherence trajectories would be beneficial to clinicians to plan targeted and personalized interventions to promote adherence. Further, identification of patients who may have difficulty adhering to dietary interventions should result in better treatment-to-patient matching, improved adherence promotion efforts, and cost savings. Indeed, alternative approaches to treatment could be considered prior to determining that a patient had been non-adherent to treatment recommendations for a long period of time. For example, a patient who has difficulty adhering to a granular form of a supplement might be prescribed a pill form of that supplement rather than mixing it with other foods to improve palatability. While this would require a substantial number of capsules to be taken, it may still be preferable for some patients and result in better adherence.

The adherence findings from this study should be considered in light of a few methodological limitations. First, the best, most objective measure of adherence available was employed: packet counts. Nevertheless, this process required vigilance and cooperation from the participants, parents, and study team to ensure an accurate count. Also, as with any measure of adherence, there is measurement error that can be introduced (e.g., packet was emptied but supplement was not consumed, packets were lost, etc.), though these instances are rare. Further, parent count of remaining packets was used rather than mailing remaining packets to the study site to reduce burden on participants. This approach for obtaining count data for adherence has been shown to be reliable (Pieper, Rapoff, Purviance, & Lindsley, 1989). Ideally, electronic monitoring of adherence would be used; however, no commercially available electronic monitoring device at the time offered the ability to measure this type of supplement use accurately while preserving the ingredients stability. Additionally, group-based trajectory modeling was used to analyze the data, which was appropriate for the sample size. However, with a larger sample size, a growth mixture modeling analytic approach, which allows for continuous examination of variables as opposed to categorical, could be used.

Continued investigation of assessment and promotion of dietary adherence in CF care is warranted, particularly as new products and approaches are developed. Daily adherence data would be optimal to identify the specific timing of adherence intervention and its impact on supplement adherence. Efficacious adherence intervention approaches including behavioral, cognitive-behavioral, individual, and family-based interventions could be provided to patients and their caregivers. Additionally, models of adherence intervention delivery that minimize patient and family burden are needed as these families are typically over-burdened with treatment demands required for patients with CF and PI. Telehealth and eHealth options provide more flexibility and the potential for minimizing personnel resources to deliver treatment to a larger number of patients. For example, all patients could receive regular pre-programmed web-based adherence intervention. Those who demonstrate poor adherence are then provided more intensive, individualized intervention via telehealth or in person. Additionally, predictors of poor adherence should be examined. For example, parental feeding styles, parent-child interactions, and behavioral strategies at mealtimes can impact dietary adherence, particularly for young children. Family stress, socioeconomic status, and family functioning are also important variables to consider. Finally, cost analyses of providing adherence interventions are needed, with the impact on adherence and associated short- and long-term health outcomes considered.

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CRediT authorship contribution statement

Kevin A. Hommel: Conceptualization, Formal analysis, Investigation, Methodology, Resources, Supervision, Visualization, Writing - original draft. **Joseph Rausch:** Formal analysis, Methodology, Software, Writing - review & editing. **Elizabeth K. Towner:** Investigation, Writing - review & editing. **Joan Schall:** Methodology, Writing - review & editing. **Asim Maqbool:** Writing - review & editing. **Maria Mascarenhas:** Writing - review & editing. **Virginia Stallings:** Investigation, Methodology, Resources, Funding acquisition, Writing - review & editing.

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