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Adults With Cystic Fibrosis: Self-Management And Health Outcomes

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This dissertation is comprised of three manuscripts reporting on adults living with cystic fibrosis (CF), self-management behaviors and health outcomes. Chapter I explores what is known about adults living with CF and the factors impacting their self-management, including the complexities of a health maintenance regime required for survival while integrating and balancing the realities of adulthood. The review of literature provides direction for future research and implications for adult-focused CF studies. Chapter II is a manuscript describing the characteristics of prognostic survival models utilized in adult CF research and provides an overview of their development, validation, predictive values, and prognostic outcomes. Models were evaluated for applicability to research and clinical practice and it is suggested a reliable prognostic survival model which is easily adaptable to research and practice exists. This prognostic survival model is highlighted further as the health outcomes measure utilized in Chapter III. In this chapter, the findings of a longitudinal, descriptive repeated measures study exploring improved health outcomes among adults living with CF who reported adherent self-management behaviors regarding their prescribed treatment plan are described. Health outcomes improved for those participants in our study who adhered to their disease modifying treatments, showing a statistically significant reduction in risk for transplant or death within the next four

years. Additional inquiry into adherence levels and barriers to maintaining adherence among adults with CF is warranted.

KEYWORDS: cystic fibrosis, adult, adherence, self-management, health outcomes

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ADULTS WITH CYSTIC FIBROSIS: SELF-MANAGEMENT AND HEALTH OUTCOMES

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CONTENTS

TABLES

FIGURES

CHAPTER I: THE IMPACT OF LIVING WITH CYSTIC FIBROSIS FOR ADULTS

Chapter I includes a review of adult cystic fibrosis literature which highlights the complexities of day to day self-management and elements influential for guiding needed research. The manuscript is planned for submission to *Chronic Illness* for publication.

Abstract

Advances in modern medicine have led to progressive treatment options and an increase in longevity for adults living with cystic fibrosis (CF). The CF community today is comprised mostly of adults, yet adult research samples routinely incorporate child and adolescent subjects or account for the caregiver, parent, or support person when discussing home management of care. The reality of adulthood may include balancing responsibilities of home, work, school, and social life and may require complete independence without the benefit of the support network many experience during childhood. Daily self-management of a complex prescribed treatment plan is required if continued treatment success and positive health outcomes are to be achieved. However, minimal literature is available describing many important dimensions including: research focused exclusive to living as an adult with CF, the factors impacting self-management, and recommendations for future research. Here, we present what is known about adults living with CF and the factors that impact self-management.

Introduction

Until recently, a diagnosis of CF rarely included survival to adulthood (Simmonds, Cullinan, & Hodson, 2009). Today, more than 53% of the CF patient population are 18 years of age or older with survival possible into the early 40's (Cystic Fibrosis Foundation, CFF, 2016a, 2017). Current advancements in genetic research, improvement in treatment, pharmaceutical enhancements, and the establishment of specialized CF care centers have all contributed to the

improved survival rates among adults living with CF (Rubin et al., 2017; Sawicki, Sellers, & Robinson, 2009). However, the success of many of these advances rely primarily on the adult CF patients' cooperation and feedback in the maintenance of a complex daily self-management regimen.

Regardless of age or symptomology, CF patients are prescribed similar health maintenance routines despite difference in personal experiences, self-management behaviors and outcomes. A number of factors are influential on disease severity and health outcomes among adults living with CF, including the socioeconomic environment, cultural and community influences, resources that mitigate stress, prescribed treatment adherence, and self-management skill (Cohen-Cymberknoh, Shoseyov, & Kerem, 2011; Sawicki et al., 2013; Schechter, 2011). However, information exclusive to the adult CF population and self-management of their disease is lacking. If researchers and clinicians hope to influence the health and wellbeing of a population which comprises over half of all those living with CF today, more insight into their lives must be provided. The purpose of this paper is to present what is known about adults living with CF and the factors that impact self-management.

Cystic Fibrosis

Cystic Fibrosis is the most common inherited genetic disease of the lungs and digestive system affecting about 30,000 people in the United States and 70,000 people worldwide, with adults being more than half of those impacted today (CFF, 2016a; 2017). The etiology of CF includes mutations of a single gene, which encodes the CF trans-membrane conductance regulator or CFTR (Hopkins, 1996). This alteration of the CFTR causes irregular sweat glands and abnormally thickened secretions of the respiratory, gastrointestinal, and reproductive tracts, which characterize the clinical symptoms of the disease (Wilmott & Fiedler, 1994). The disease

manifests itself most seriously in the lungs and pancreas. Potential complications caused by CFTR dysfunction include increased inflammatory response, defects in bacterial phagocytosis, changes in antimicrobial properties of airway mucus, and susceptibility to opportunistic bacteria, all of which are associated with shortened survival (Terheggen-Lagro, Rijkers, & van der Ent, 2005; Li et al., 2005). Those with CF may experience mild gastrointestinal (GI) or pulmonary problems, whereas others may experience severe malabsorption problems and fatal pulmonary complications (Carpenter & Narsavage, 2004). This incurable, progressive, multisystem disease harms numerous organs, complicates many of the body's normal processes, and shortens life expectancy.

Daily Management

Living with CF requires daily management of the disease and symptom manifestations. Outcomes and disease progression vary among adults living with CF, which stresses the importance of understanding self-management of a chronic illness among populations who essentially 'grew up' with a chronic illness. Many adults living with CF today are college graduates, working, establishing relationships, becoming parents, and leading independent lives (Al-Yateem, 2012; CFF, 2016a).

Transition is a unique process experienced only by those populations afflicted with a chronic illness throughout multiple developmental stages of life. It is a vital component to the progression and development of self-management behaviors and skills, which makes it key to the phenomenon of adherence among adults with CF. Transition has been identified as a significant period in the life of young adults with CF, as well as other chronic illness sufferers (Al-Yateem, 2012; Lotstein, 2009; Towns & Bell, 2011). Those with chronic illness who are reaching adulthood require age-appropriate care and counseling regarding adult-focused concerns, such as

self-management, employment, and reproduction (Duguépéroux et al., 2008). Support is vital during this stressful time and is associated with better post-transition outcomes. Better self-management behavior has been found among those who attend chronic disease support groups (Chiou, 2014). However, within the CF community, opportunities for personal interaction between patients for education or mutual support are not generally feasible due to possibility of cross-contamination with resistant pulmonary bacteria (Tuchman, Schwartz, Sawicki, & Britto, 2010).

People with chronic illness differ in their readiness and abilities to spend time, energy, and focus on their illness at varying points in their lives (Clark & Gong, 2000; Hwu & Chin-Ching, 2006). Adults living with CF are dependent on daily self-management for continued quality and quantity of life, however, it is commonplace to identify variability in self-management behavior, such as, adherence to all prescribed treatment plan recommendations (Abbot, Dodd, Bilton, & Webb (1994); Conway, Pond, Hamnett, & Watson (1996); O'Sullivan, Sullivan, Higuchi, & Montgomery (2011).

The usual recommended treatment includes multiple inhaled therapies, airway clearance two times per day, oral medications, and boosting calories to 110% to 220% of the recommended daily allowance (Quittner et al., 2012). The time-consuming daily regimen involves completing several health maintenance treatments (Figure 1), maintaining weight, and engaging in aerobic activities. For adults living with CF, self-care behaviors may include performing chest physiotherapy, use of airway clearance devices, taking prescribed medications, and monitoring respiratory and nutritional status (Baker & Denyes, 2008; Hockenberry & Wilson, 2013).

Diagnosis of CF generally occurs early, usually within the first years of life, so health management must begin during infancy. Ideally, as one grows up with CF, responsibility for

maintaining the health and treatment regimen gradually transitions from the family members to the child. Children with CF must learn to recognize and treat symptoms as well as signs of serious pulmonary exacerbations (Quittner, Espelage, Levers-Landis, & Drotar, 2000b).

Aggressive and arduous CF treatment regimens are required on a daily basis, as the child with CF becomes aware that failure to manage the prescribed treatments and medications adequately can quickly lead to serious decline (Li et al., 2005). Research participants have expressed difficulty in physically integrating the practicalities involved in managing a recommended healthcare regimen into a busy lifestyle (Badlan, 2007).

Adherence to prescribed treatments among those with chronic illness is a global issue and not just a need to label patients as compliant or noncompliant. It is a problem of humans in general. Adherence itself needs reframed and rethought to be one of the most challenging areas of chronic disease management (Wildman & Hoo, 2014). Overall, it is estimated that adherence rates are 30-50% among the general population (Wildman & Hoo, 2014) and 35-75% among users of chronic pulmonary medication, depending on drug and age (Eakin et al., 2011; Daniels et al., 2011). Within primary care, at least $300 million worth of medicines are wasted due to poor adherence for self-care management by those with chronic conditions, such as asthma (Horne & Weinmann, 2002).

Recently, researchers undertook the task of standardizing methods for reporting adherence to inhaled therapies among adults with CF (Hoo et al, 2016). The lack of evidence affirming how much adherence is enough among adults with CF makes determination of this standard an ongoing process (Kettler, Sawyer, Winefield, & Greville, 2002). The recent work being done to accurately calculate adherence is needed even beyond inhaled therapy and should be expanded into determining minimum necessary adherence for each portion of prescribed

treatments and medications. Researchers must ask themselves, for each portion of a prescribed treatment plan, what is the appropriate 'dose' to be adherent.

Impact of Adherence

Researchers and clinicians believe the impact of self-management skills, including adherence to prescribed treatment plans among adults living with CF, explains the significant variation in patient outcomes (Schechter, 2011; Schechter & Gutierrez, 2010; Zemanick et al., 2010). Severity of lung disease is the key to length and quality of life among patients with CF (van Gool et al., 2013). Researchers suggest poor self-management skill is associated with exacerbation of pulmonary dysfunction and lower baseline lung function (Eakin & Reikert, 2013; Eakin, Bilderback, Boyle, Mogayzel, & Riekert, 2011). Adherence rates among adults with CF are similar to those living with other chronic illnesses (Kettler et al., 2002; Sawicki et al., 2009). However, adults living with CF require adherence to a variable and involved daily regimen, frequent follow up visits with multiple health specialists, and constant self-monitoring, entailing necessity of multiple adherent behaviors in addition to navigating the common daily stressors of adulthood. Limited empirical evidence regarding adherence as it relates to health outcomes among adults living with CF constrains the ability of health professionals to make the needed population sensitive recommendations or offer interventions which lessen patient burden related to self-management behavior.

At times, patients with a chronic and/or terminal illness may consider self-management futile. Cystic fibrosis is a progressive illness, but in a study on CF treatment, where the researchers assumed patients did not improve their health state, 83 of their 2255 (0.03%) enrolled subjects did improve lung function over a three-year time frame (van Gool et al., 2013). Self-

management behaviors may influence the variability in disease progression and health outcomes among those living with CF.

There is a gap between current treatment success rates and those believed to be achievable among chronic disease sufferers in the United States; this gap has been attributed in part to issues with self-management and lack of patients' ability to adhere to recommendations (Institute of Medicine [IOM], 2003; Viswanathan et al., 2012). One reason thought to contribute to problems with self-management of chronic disease was treatment costs. The average annual cost for individual CF treatment is more than $40,000 accumulating to approximately $306, 332 over a lifetime, with the majority of costs consisting of hospital admissions (58%), followed by pharmaceuticals (29%), medical services (10%), complications (2%), and diagnostic testing (1%) (CFF, 2012; Lieu et al., 1999; van Gool et al., 2013, Rubin et al, 2017). The CFF (2012) stated that one in four CF patients skipped doses of their medicine or purposefully took smaller doses because of cost, and nearly one in five delay seeking care for the same reason.

Although it is established that adherence influences outcomes, evidence is limited on whether approaches to improve adherence are broadly applicable or affect long-term adherence and health outcomes (Viswanathan et al., 2012). Among CF patients six years of age and older, researchers found poor adherence to nebulized medication as a significant predictor of having a pulmonary exacerbation requiring intravenous (IV) antibiotic therapy (Eakin et al., 2011). Researchers report lower baseline lung function (Eakin et al., 2011), higher costs (Nasr, Chous, Villa, Chang, & Broder, 2013), and increased hospitalizations (Briesacher et al., 2011) are associated with poor adherence to CF medication therapy. CF researchers have limited studies to one medication or therapy and included children and adolescents, as well as adults. This highlights the need for continued inquiry specifically targeting the adult CF population and

integrating the variable adult CF treatment regimen into data collections and analysis to add to a lacking body of knowledge regarding adherence and health outcomes.

Financial Impact

Funding and affordability of treatment programs designed for adults living with CF remains a challenge. Insurance coverage plays a significant role in the health and wellbeing of people living with chronic illness in the United States. In 2010, the Patient Protection and Affordable Care Act (ACA) was signed into law in the United States (Lyon, Douglas, & Cooke, 2014). Due to the ACA prohibiting pre-existing condition penalties or benefit ceilings, and its push for expansion in state Medicaid coverage, it seemed as though the ACA was going to be of significant benefit to those living with CF. However, the CF population and their healthcare providers are experiencing continued difficulty with the U.S. healthcare system (Nathanson, Ramírez-Garnica, & Wiltrout, 2005; O'Sullivan et al., 2011). While the Medicaid expansion is an important step toward limiting insurance-related disparities, studies have shown poorer outcomes among patients with lung disease who utilize Medicaid compared with those enrolled in private insurance. (Slatore, 2010; Lyon et al., 2014). Advocacy for improvement in policies and support for inclusive health insurance expansions within the research arena may have the potential to facilitate advancement in health outcomes and reduce barriers for patients and practitioners within the CF community.

Chronic illness often interferes with maintaining continuous full-time employment, thus limiting access to private health insurance. In addition, complex medical treatment results in reaching maximum lifetime insurance benefits. The CFF found among those living with CF, half are spending at least $300 on insurance premiums and at least $200 on out-of-pocket costs for CF-related medication, 14% had reached their annual limit on insurance coverage, and 3% had

reached their lifetime limit (CFF, 2012; CFF, n.d.). According to researchers who reported the yearly expense for all medical necessities, the average annual cost of survival for a person living with CF is $46,000 (Ouyang, Grosse, Amendah, & Schechter, 2009). However, a CF patient has the potential for unpredictable exacerbation requiring increased medication usage and hospitalizations. In a recent study, annual costs associated only with worsening lung symptoms among patients ranged from $30,066 to $119,862 (Rubin et al, 2017).

National guidelines recommend CF patients attend outpatient appointments at least once every four months (CFF, 2016a). Nathanson and colleagues (2005) suggested those with managed care, or requiring a referral prior to seeing a specialist, may not have equal access to experts in CF, as managed care patients attended appointments significantly less frequently than those in non-managed care, thus were not seeing their CF specialized healthcare provider as often as recommended, or not at all. The ACA allows for variability in what is termed, 'essential health benefits' when expanding state Medicaid coverage. This may interrupt care services and treatment for patients with pulmonary diseases, including CF, who utilize Medicaid.

The new essential health benefits may limit who is deemed an essential provider, limiting access to CF specialists, and it does not guarantee access to all of the medication determined to be necessary in individual cases. Instead, it allows allocation of a specific number of medications in each drug class, limiting a provider's choice in treatment or a patient's ability to afford needed prescriptions (Cheng, Wise, & Halfon, 2014; Kraft, 2012; Lyon et al., 2014). This can be devastating for CF patients' prognosis as many of their critical medications lack a cheaper, generic alternative. Combination medications, such as those prescribed for inhalers and nebulizers, are also not provided for in the current ACA law, which may threaten the health of adults living with CF, as these therapies are required several times daily to limit deadly lung

exacerbation (Billings, 2013; Kraft, 2012; Lyon et al., 2011). Additionally, necessary durable medical equipment, such as nebulizers, interpretation of pulmonary function tests, counseling for end-of-life, and palliative care are not included in the minimum benefit standards for Medicaid or Medicare recipients (Bisgaier & Rhodes, 2011; Kraft, 2012).

Biological and Psychological Impact

CF contributes to impaired physical functioning, loss of independence, emotional distress, and changes in self-identity (Badlan, 2007; CFF, 2016a; Simmonds et al., 2009). In addition to frequent illness, persons with CF face many serious problems in daily living, in some instances due to physical limitations caused by pain. Hubbard, Broome, & Antia, 2005). In one study, 55.6% of participants with CF reported pain on a daily basis (Hubbard, Broome & Antia, 2005; Sawicki et al., 2009; Simmonds et al., 2009). Adults with CF live with the reality that their diagnosis is progressive and fatal. As life expectancy is well documented, adults living with CF must face their mortality early and may either learn to appreciate life more and participate in their healthcare, (Peterson, 2006), or it may cause the person to feel powerless and lack motivation to contribute to their own wellbeing (Carpenter & Narsavage, 2004). Researchers studying hopes and fears among adults living with CF discovered, in addition to worry surrounding premature death and potential suffering, participants had hopes of experiencing normal relationships, child rearing, and employment (Higham, Ahmed, & Ahmed, 2013). CF, as a chronic illness with no current available cure, imposes a tremendous burden on the individual's physical and mental wellbeing. Researchers need to remain mindful of these facts when developing questions and conducting studies.

Social and Cultural Impact

Adults living with CF may choose to attend college, become employed, marry or have families. They do so despite the challenges created by their illness. Genetic conditions like CF may be stigmatizing or involve feelings of shame and embarrassment within the family structure (Simmonds et al., 2009). The experience of social exclusion is reported frequently (Peterson, 2006). The weight CF has on influencing patients' decisions to engage in social activities, like travel, play with one's own children, or sports is significant (Simmonds et al., 2009). Many believe these activities could pose a threat to their fragile state of health. Adults with CF describe the unpredictability of symptoms and treatment regimens and the impact on life plans (Simmonds et al., 2009). People are often forced to reassess their priorities in life, and in some cases, 'plan for the worst' (Peterson, 2006).

Numerous factors burden adults living with CF and influence their physical, psychological, social, and vocational wellbeing. Researchers among this population must consider these influencing factors when making decisions regarding needed studies, determining research burden for participants, and controlling for variable in outcomes research.

Needed Research

The chronic nature of CF may influence the quality and quantity of life among adults living with CF and limited research regarding this phenomenon prompts a pressing need to increase adult CF nursing research. Specifically, adherence research about patients who self-manage may provide needed insight into the nature of health challenges for patients with CF, perhaps facilitating the provider's ability to give the best care (Riegel, Jaarsma, & Stromberg, 2012). Although research among adults with CF is emerging, much of the self-management

research is lacking an association to health outcomes and those that do, are either not exclusive to adults with CF, or are limited to adherence of one aspect of the prescribed treatment plan.

Measurement of adherence is a vital component to self-management research, however many researchers are reporting difficulty (Eakin et al., 2011; Faulkner, Taper, & Scott, 2012; Kettler et al., 2002; Viswanathan et al., 2012). Many measurement tools developed for CF research must be modified for use among the adult population or simply do not exist. Objective measures for adherence are preferred but feasibility is questionable as Medication Event Monitoring Systems (MEMS) are costly. Safe guards are non-existent to ensure patients are adherent to the prescribed regimen and not just accessing medication vials, nebulizers, and vest machines, but whether they are actually utilizing them. Self-report discrepancies can often be interpreted as patients attempting to deceive, but can reflect simple difficulties in recollection (Wildman & Hoo, 2014). A careful review of literature warrants a need for development of a reliable and valid, yet publicly available, tool that is able to distinguish the level of adherence. Pharmaceutical refill counts are a promising objective measure, but again, there lacks certainty the medication is utilized after it is filled and the patients' pharmacy is involved with only portions of the recommended treatment regimen for adult CF patients (Wildman & Hoo, 2014). Feasibility and intervention studies utilizing adherence and self-management technology among adult CF patients may be vital to improving data collection.

Improved understanding of the theoretical knowledge that underpins the complexities of adherence among the aging population may benefit the CF community (Banning, 2009). An important next step is to examine the relationship between adherence trajectories and health outcomes, including pulmonary functioning, nutritional status, and health-related quality of life. Researchers must identify optimal levels of adherence, which may promote the best health

outcomes (Modi et al., 2010). There is little known research about the relationship between level of adherence to a prescribed regimen and health outcomes among adults living with CF. This is of significant concern as researchers find adherence to medications is poor among people with CF (Eakin et al., 2011; Cohen-Cymberknoh et al., 2011). Poor adherence may be associated with accelerated decline in lung function and the need for increased interventions (Eakin & Reikert, 2013).

Treatment complexity coupled with barriers to self-management of chronic illness experienced by adults with CF result in varying levels of adherence. The treatment demands placed upon adults with CF are extraordinary when compared with most other chronic illnesses (Kettler et al., 2002). Research into dynamics of treatment burden and perceived burden overtime and the effect on self-management in adults with and without changes in treatment complexity would be of considerable research interest to the CF community (Sawicki et al., 2013). In addition, given the lack of agreement among CF specialists and healthcare teams regarding which treatments are most important, further research interpreting and determining the priority of adherence to each treatment within the health maintenance regimen would be of significant importance (Quittner et al., 2000a; Kettler et al., 2002). Efforts to quantify necessary adherence may facilitate development of more manageable prescribed treatment plans and limit patient perceived burden.

As adults living with CF face new challenges, additional research is needed to examine how patients participate in management of their CF over the long term (Carpenter & Narsavage, 2004). New policies for training skills in self-management and health literacy using collaborative models are needed, especially as adult CF patients attempt to maneuver independently within a complicated healthcare system (James, Boyle, Bennett, & Bennett, 2012; Lloyd, Ammary,

Epstein, Johnson, & Rhee, 2006). More research is needed to support the policy change needed to impact and introduce adult focused initiatives for CF.

Future researchers may provide needed information to health care professionals in order to promote and facilitate self-management among the adult CF population. Examining the motivational attributes present in the self-managing adult with chronic illness experiencing desired outcomes would be beneficial for guiding person-centered interventions. Costs and benefits of technology for self-management of chronic illness are necessary for future research (Stellefson et al., 2013). Utilization of technology for personal health databases in self-management of CF could be an important contribution. Research focusing on the specific nature and meaning of the experiences among adults living with CF is necessary. The potential exists to improve the quality and quantity of life among this vulnerable population by exploring research questions pertinent to their needs**.**

Conclusion

Advances in health care have extended the lives of those living with CF into adulthood resulting in transition from dependence upon caregivers and pediatric care settings to self-management of symptoms and participation in treatment planning. The chronic nature of CF requires self-management, which may influence the quality of life and health outcomes among adults living with CF. Limited research regarding the adult living with CF prompts a pressing need for researchers to explore phenomena utilizing exclusively adult samples. As adults living with CF face new challenges, such as, issues surrounding healthcare access, disclosure of their disease, education, employment, marriage, childbirth, and end-of-life decisions, understanding the experiences of adults living with CF is necessary. An aging CF population requires continuous self-management and adherence to multiple daily treatments and medications,

therefore, evidence-based recommendations addressing the adult CF population may impact societal and economic burdens, preventable hospital admissions, morbidity, and mortality. Researchers who focus on adults living with CF, may provide needed insight into the nature of health challenges, facilitating the ability to provide the best care (Riegel et al., 2012).

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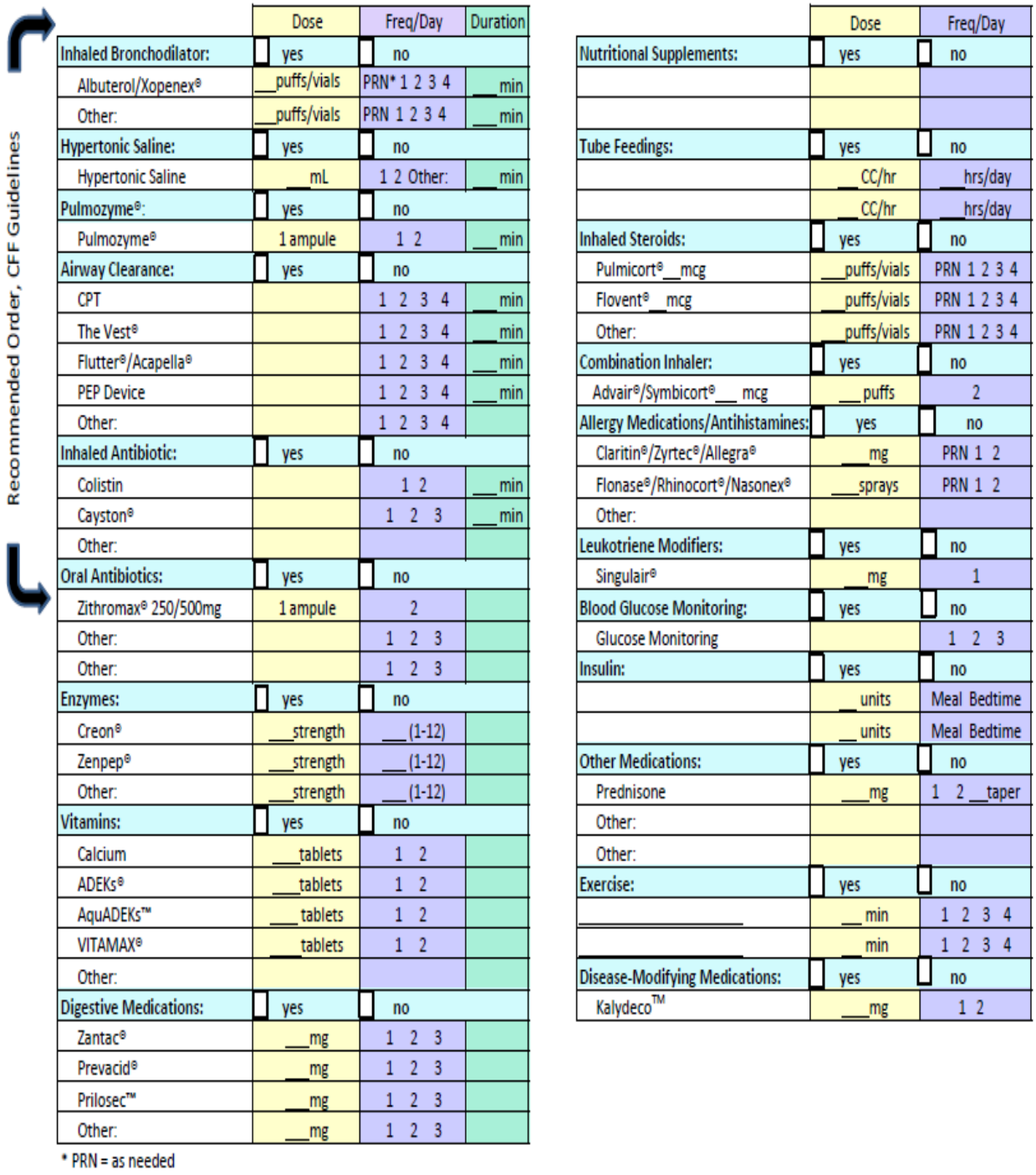

Figure 1. Typical daily adult CF health maintenance requirements and frequency. Prescribed Treatment Plan, by Quittner, A. L., 2000, Retrieved from http://www.psy.miami.edu/ksa_measures/pub.phtml. Copyright [2011] University of Miami. Reprinted with permission.

CHAPTER II: EVALUATION OF PROGNOSTIC SURVIVAL MODELS FOR ADULTS WITH CYSTIC FIBROSIS

Chapter II is systematic review of prognostic survival models utilized in CF research. Advances in genetics as well as other breakthroughs in clinical research warrants the determination of reliable, functional, and adult-focused measurement tools. The manuscript will be submitted for publication to *Journal of Cystic Fibrosis,* or *Respiratory Care;* or *Chronic Illness*

Abstract

Indicators of mortality combined for the construction of prognostic models can assist clinicians with individualized treatment, validation of current therapy, self-management, optimization of transplant timing, and determination for end of life discussions and planning, however a widely-accepted model for adults with cystic fibrosis (CF) does not exist. A systematic review was conducted to evaluate prognostic survival models for use among adults with CF. We conducted a literature search for studies published between 1990 – 2017 in the PubMed, CINAHL, OVID, ProQuest and Google Scholar databases that described development of prognostic models of survival for CF patients utilizing more than one clinical indicator. 127 articles were identified and after applying our inclusion and exclusion criteria, six articles remained for further evaluation. Most researchers utilized CF patient registry data and variable clinical indicators among samples of combined pediatric and adult patients to develop prognostic survival models. Characteristics of prognostic survival models, ease of use, and applicability to research and clinical practice among adults with CF were identified. Of the models reviewed, one, the CF-ABLE, lends itself to ease and applicability to adult CF clinicians and researchers. Future research should include development of models inclusive of clinical determinants

reflective of the latest prognostic factors among adult CF outcomes research and be validated among different national registries and their contributing centers.

Introduction

Cystic fibrosis of the pancreas was first characterized by Dr. D.H. Anderson in 1938. Since that time, over 1,700 mutations of the CF transmembrane conductance regulator, or CFTR gene, have been recorded (CFF, n.d.). Researchers have identified and reported numerous clinical indicators that impact the disease severity and prognosis (CFF, 2016). The flawed CFTR gene contributes to the complications of many organ processes among patients with CF, thus accounting for differences in clinical presentations and severities of the disease (Carpenter& Narsavage, 2004). Health outcomes, as well as clinical indicators of prognosis vary greatly. After decades of research and clinical advancements, agreement among CF researchers regarding which health indicators and at what level of physical functioning both the clinician and patient should base their health management decisions has yet to be determined; nor has a simplistic prognostic measure been widely accepted.

Clinical Determinants

Determinants of mortality among patients with CF have been established and clinical deterioration and progression to death among CF patients has also been attributed to lung infection and colonization by microbials (Courtney et al., 2007; Dasenbrook, Konstan, & VanDevanter, 2015; Kalish et al., 2006), frequency of pulmonary exacerbation (Dasenbrook et al., 2015; Kanga, Kuhn, Craigmyle, Haverstock, & Church, 1999), CF-related diabetes (Adler, Shine, Haworth, Leelarathna, & Bilton, 2011; Kerem, Reisman, Corey, Canny, & Levison, 1992), gender (Kerem et al., 1992), phenotype (Hafen et al., 2008) and nutrition (Courtney et al., 2007; Fogarty, Britton, Clayton, & Smyth, 2012.)

A recent 7-year follow up study among a cohort of adults living with CF identified pulmonary artery systolic pressure ≥42 mm Hg and Forced Expiratory Volume or FEV1of ≤30% were significant predictors of poor outcomes (Flores et al., 2016). There is general agreement that respiratory decline, specifically a reduction in FEV1, is the leading prognostic indicator of survival among CF patients (Kerem et al., 1992; Sanders, Bittner, Rosenfeld, Redding, & Goss, 2011; Yankaskas & Mallory, 1998).

Disease Severity Scores

Scoring systems were first introduced to identify disease severity and assist clinicians and guide decisions about treatment protocols (Shwachman & Kulczycki, 1958). These scoring systems were subjective and progressed slowly, with only a slight modification introduced by Doershuk and colleagues (1964) due to the phenomenon of increased survival among those with CF. Clinicians and researchers were limited to the subjective scoring systems prior to the development of the simplified CF scoring system (SCS), which was the first objective clinical scoring system for CF patients (Cooperman, Park, & McKee, 1971). The SCS (1971) was weighted heavily on lung health, which aligns with today's standard of noting pulmonary decline as a primary diagnostic and prognostic measure of health outcomes (Dodge, Lewis, Stanton, & Wilsher, 2007). However, with the SCS only including two activity scores ("*engages in athletics with normal peers"*, and "*misses not more than 2 school days per month"*) (Cooperman et al., 1971), this historical scoring system is outdated for both the current primary adult CF population and known indicators of disease progression. Modern disease severity scoring systems have been constructed to reflect that CF is an autosomal recessive genetic disorder (CFF, 2016). Researchers have adapted these tools to account for phenotype expressions (Hafen, et al., 2008).

Variability among CF patients' clinical presentation and an aging adult CF population prompts inclusion of known predictors of survival in addition to lung function when conducting outcomes research. Additionally, statistically significant indicators of mortality should be combined for the construction of prognostic models as they may assist clinicians with individualized treatment, validation of current therapy and self-management, optimization of transplant timing, or determination for end of life discussions and planning (Dodge et al., 2007); Flores et al., 2016).

The purpose of this paper is to evaluate the prognostic survival model systems for adults with CF. Specifically, we aim to describe the characteristics of the CF prognostic models and their indicators of survival, ease of use, and applicability to research and clinical practice.

Methods

We completed an electronic search of PubMed, CINAHL, OVID, ProQuest and Google Scholar databases and included search terms "cystic fibrosis", "prognostic", "adult", and "predicted survival". The location of the CFTR gene was first disseminated to the research community in 1989, therefore, database searches included articles published 1990-2017.One hundred and twenty-four citations were located. A hand search of references provided 16 additional articles. After removal of duplicates, a total of 127 abstracts were reviewed (Figure 2).

Inclusion and Exclusion Criteria

Articles written in English in which more than one clinical determinant of disease severity and prognosis were combined in the construction of a predictive model or score were included along with researchers reporting on the generation of a new prognostic model. Hayllar et al. (1997), included patient data collected between 1969 through 1987. Studies where the

majority of data was collected before1990 were excluded. Validation only studies were also excluded from evaluation. Studies without adult population samples were also excluded.

Results

Following appraisal of inclusion and exclusion criteria, full print copies and any available supplemental materials of the final six articles were obtained for evaluation. We identified the following information: first author, country, journal, publication year, study sample, validation sample, clinical indicators selected, predictive value, and prognostic outcome.

Characteristics of the Literature

A summary of the research evaluated is displayed in Table 1. The publications extend sixteen years from 2001 to 2017, representing CF patient data collected as early as 1986. Since the discovery of the CFTR gene, researchers have developed models from CF populations in several countries including one each from Canada (Aaron, Stephenson, Cameron, & Whitmore, 2015), France (Nkam et al., 2017), Ireland (McCarthy, Dimitrov, Meurling, Gunaratnam, & McElvaney, 2013), and Italy (Buzzetti et al., 2011), and two from the United States (Liou et al., 2001; Mayer-Hamblett, Rosenfeld, Emerson, Goss, & Aitken, 2002.)

Sample sizes ranged between 49 patients from a single center to over 14,000 patients from registry data collected from more than 100 CF centers spanning an entire country. Researchers included both pediatric and adults during development of four prognostic models reviewed (Aaron et al., 2015; Buzzetti et al., 2011; Liou et al., 2001; Mayor-Hamblett et al., 2002), with their subjects ranging in age from three to 62 years of age. Researchers included adult-only samples in two models reviewed (McCarthy et al., 2013; Nkam et al., 2017) with subjects ranging 20 to 32 years of age. Model validation procedures implemented by the

researchers during testing of each of the prognostic models is outlined in Table 2. Only one of the prognostic models reviewed utilized external validation methods (McCarthy et al., 2013).

We reviewed the models' study samples, development, validation, the researchers' choice and variability of clinical indicators selected, and the ease by which clinicians may translate use of the prognostic survival model to research or practice. Models with predictive values of 1 year (Aaron, et al., 2015), 2 years (Mayer-Hamblett et al., 2002), 3 years (Nkam et al., 2017), 4 years (McCarthy et al., 2013), and 5 years (Buzzetti et al., 2011; Liou et al., 2001) , with prognostic outcomes of survival (Aaron et al., 2015; Buzzetti et al., 2011; Liou et al., 2001; Mayer-Hamblett et al., 2002; McCarthy et al., 2013; Nkam et al., 2017), exacerbation (Aaron et al., 2015), and transplant referral Mayer-Hamblett et al., 2002; McCarthy et al., 2013; Nkam et al., 2017) were developed and evaluated.

Lung function alone guided models predicting risk previously, however, researchers incorporated several commonly measured clinical indicators in the studies we reviewed. Statistically significant clinical indicators included, age (Aaron et al., 2015; Liou et al., 2001; Mayer-Hamblett et al., 2002; McCarthy et al., 2013), age at diagnosis (Aaron et al., 2015), gender (Aaron et al., 2015; Liou et al., 2001), delta F508 mutation (Aaron et al., 2015), height (Mayer-Hamblett et al., 2002), body mass index or BMI (Aaron et al., 2015; McCarthy et al., 2013; Nkam et al., 2017), and weight (Aaron et al., 2015; Liou et al., 2001).

Clinical indicators associated with pulmonary status included exacerbation (Aaron et al., 2015; Buzzetti et al., 2011; Liou et al., 2001; Nkam et al., 2017; Mayer-Hamblett et al., 2002), FEV_1 % predicted (Aaron et al., 2015; Buzzetti et al., 2011; Liou et al., 2001; Mayer-Hamblett et al., 2002; McCarthy et al., 2013; Nkam et al., 2017), long-term oxygen therapy (Nkam et al., 2017), lung function (Aaron et al., 2015), and non-invasive ventilation (Nkam et al., 2017).

Clinical indicators identified by organism included *P. aeruginosa* colonization (Aaron et al., 2015; Mayer-Hamblett et al., 2002), and *S. aureus* colonization (Buzzetti et al., 2011; Liou et al., 2001), and *B. cepacia* colonization (Buzzetti et al., 2011; Liou et al., 2001; Mayer-Hamblett et al., 2002; Nkam et al., 2017).

Clinical indicators associated with medication comprised of IV antibiotics (Mayer-Hamblett et al., 2002; McCarthy et al., 2013; Nkam et al., 2017) and oral corticosteroids (Nkam et al., 2017). Other clinical indicators included diabetes (Aaron et al., 2015; Liou et al., 2001), and pancreatic insufficiency/sufficiency (Aaron et al., 2015; Liou et al., 2001).

Ease of Use

The six prognostic models reviewed included two that could be calculated independent of statistical analysis software (Liou et al., 2001; McCarthy et al., 2013). Liou and colleagues (2001), provide worksheets on the publication's journal website to assist clinicians with calculating the five year survival prediction for one patient. The worksheets encompass twenty steps of entering the nine patient clinical indicators or outcomes for tabulation into a 'raw score' that corresponds with a percent prediction of survival in increments of five from 5-95% (Liou et al., 2001).

McCarthy and colleagues (2013) constructed an 'ABLE score' (age, BMI, lung function, and exacerbations) which clinicians and researchers can hand-tabulate by inputting the sums from each of the four clinical indicators and adding the assigned scores from the model (Table 3). Patients who score >5 have a greater risk of poor outcomes within four years and may be identified as in need of early intervention or alternative care needs (McCarthy et al., 2013).

Applicability to Research and Practice

All of the models reviewed were objective measures and as such, are more robust against researcher, clinician, or patient bias. Of the six prognostic models reviewed, the CF-ABLE is one of two that can be scored independently of statistical software. This in addition to its utilization of everyday clinical parameters and the collection of both local electronic medical record and national patient registry data exclusively among adults with CF to develop and validate the CF-ABLE, make it a beneficial prognostic tool for use in both adult CF research and clinical practice. The ease of utilization within the complex workflow of the clinical setting is an important asset for practitioners, as it may increase the likelihood of accurate and thorough administration and completion of a prognostic model.

The CF-ABLE is more clinician friendly as it examines four clinical indicators in comparison to the 5-year survivorship model by Liou and colleagues (2001) that includes nine clinical indicators and outlines a process including upwards of 20-steps, which may need to be hand tabulated if readily available statistical software is not an option. The CF-ABLE includes clinical indicators that are attainable at clinic visits during a history and physical assessment and an easily and frequently administered lung function test result. The CF-ABLE scores are simple and cost effective and include tabulation instructions published with their supplemental materials.

The CF-ABLE model lends itself to clinicians and researchers interested in CF outcomes as its clinical indicators account for lung health, nutrition, and age, all of which are common indicators of CF health outcomes (CFF, 2016). McCarthy and colleagues (2013) developed the CF-ABLE model utilizing an adult only sample and with adults accounting for over half of the

CF population today, the CF-ABLE's development was more aligned with today's researcher and clinician.

The CF-ABLE is simplistic in clinical indicator selection, score tabulation, and prognostic evaluation for ease of translation; therefore, adult patients are better able to understand the applicability and meaning of this prognostic scoring method. Ease of use can assist the clinician with involving adult CF patients in care participation and facilitate disease specific education as well as motivational interviewing for patient-directed goal setting.

Discussion

We described the characteristics of prognostic survival model systems and provided an overview of model development, validation, predictive values, and prognostic outcomes. We also evaluated the models for applicability to research and clinical practice among adults with CF.

The 5-year survivorship model (Liou et al., 2001) and the CF-ABLE score (McCarthy et al., 2013) were found to be adaptable to the clinician's or researcher's ability to easily obtain data from clinical settings and their prognostic values could be tabulated without the need for statistical software. Both of these models were variable in clinical indicator selection, although only the CF-ABLE was exclusive to the adult population during development and validation.

Five of six studies utilized a CF patient registry in their development or validation of the models (Aaron et al., 2015; Liou et al., 2001; Mayer-Hamblett et al., 2002; McCarthy et al., 2013; & Nkam et al., 2017), thus increasing the available sample sizes and adding to the statistical significance and accuracy of the prognostic survival models. During development of the "parsimonious model", Buzzetti and colleagues (2012) limited their clinical indicators to only those having an interaction with lung function. The other five prognostic models reviewed

included varying combinations of clinical indictors. Therefore, generalizability of the prognostic models reviewed for clinicians and researchers interested in outcomes research among adults with CF may be challenging without first clearly understanding the relationship between the intended goals of their endeavor and limitations of their measurement capabilities.

All of the models evaluated included clinical indicators that can be objectively measured. Including self-reported measures may assist researchers and clinicians with capturing patient perception information, thereby potentially improving the sensitivity of models for predicating exacerbation frequency, while providing insight into transplant referral and survival. Researchers, who have studied aspects of patient-reported health-related quality of life, determined items on a subjective questionnaire in the domains of physical functioning, "*My CF has prevented me from getting out of the house to run errands"*, pain, "*How much did pain interfere with your normal work (including work both outside the home and at home)"*, and social functioning, *"I find that the way in which CF affects my socializing interferes with my overall enjoyment of life"*, along with changes in health predicted survival, *"Compared to one-year ago, how would you rate your health in general now",* served as prognostic indicators of survival among CF sufferers in the U.K. (Abbott et al., 2009). Similarly and more recently, the physical functioning and health perception scales of the patient-reported CF Questionnaire (CFQ-R) showed promising results as reliable indicators of mortality (Sole et al., 2016).

Limitations

This review is not without limitations. First, the review was limited to studies published in English and therefore may have excluded relevant articles from evaluation. All but one study utilized patient registry data which may introduce information and/or selection bias, as not all CF care centers or clinicians report their data to the national registries.

Conclusion

This review suggests a reliable prognostic survival model which is easily adaptable to research and practice exists. The majority of those living with CF worldwide are adults, therefore priority should be given to development of prognostic models that are easily applicable to adult care environments. Clinical determinants of the models should reflect the latest prognostic factors among adult CF outcomes research and be validated among different national registries and contributing centers, allowing the researchers to work collectively toward increasing the survival rate, a universal goal among the CF community.

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Table 1

Summary of Models Reviewed

First Author, Country, Journal	Publication Year	Study Sample	Validation Sample	Clinical Indicators Selected	Predictive Value	Prognostic Outcome	Score
Liou, United States *American Journal of Epidemiology*	2001	Cystic Fibrosis Foundation Patient Registry data 1986-1997 (11,630 patients *>exclusions*); Aged 5 – 62 years	Half the data set (n=5,810)	Age F EV_1 (% predicted) Gender Weight Pancreatic sufficiency Diabetes mellitus *S. aureus* infection *B. cepacia* infection Number annual pulmonary exacerbations	5 Years	Survival	5 % – 95%
Mayer-Hamblett, United States *American Journal of Respiratory and Critical Care Medicine*	2002	14,572 patients from the 1996 Cystic Fibrosis Patient Registry; Aged 14 – 34 years	10% of the study cohort (n=1400)	Number of exacerbation hospitalizations Number of home IV antibiotic courses *B. cepacia* colonization P. aeruginosa colonization F EV_1 (% predicted) Height percentile Age	2 Years	Survival Transplant referral	
Buzzetti, Italy, *Journal of Cystic Fibrosis*	2011	945 patients from 9 Italian CF centers during 2003 – 2008; Aged 9 – 27 years	patients from the study sample divided into 2 groups	F EV_1 (% predicted) Staphylococcus aureus *B. cepacia* complex Pulmonary exacerbation	5 Years	Survival	

(Table Continues)

First Author, Country, Journal	Publication Year	Study Sample	Validation Sample	Clinical Indicators Selected	Predictive Value	Prognostic Outcome	Score
McCarthy, Ireland, *CHEST*	2013	49 patients from single center over 84-months (2005–2010); Aged 20 – 22 years	370 patients from Cystic Fibrosis Registry of Ireland	Average F EV_1 (% Predicted) / last 3 months Number of IV antibiotics courses / last 3 months BMI Age	4 Years	Death Lung Transplant	*CF-ABLE Score* <u>0-7</u> < 2 (low risk) 5-7 (high risk)
Aaron, Canada, *Journal of Clinical Epidemiology*	2015	3,794 patients (44,390 visit records) in the Canadian Cystic Fibrosis Patient Data Registry up to 2010; Aged 3 – 40 years	Original data set	Lung function P. aeruginosa infection CF-related diabetes Weight Pancreatic insufficiency Delta F508 mutation Age Gender Age at diagnosis BMI Number of annual exacerbation hospitalizations Decline in F EV_1 previous year	1 Year	Survival Risk of exacerbation	<u>Intercept table:</u> CF chronic health level x Risk of severe exacerbation CF health index
Nkam, France, *Journal of Cystic Fibrosis*	2017	2096 patients in the French Cystic Fibrosis Registry from 2010 – 2013; Aged 21 – 32 years	Original data set (n = 2096)	BMI FEV_1 (% Predicted) *B. cepacia* colonization Number of IV antibiotics courses/year Number of days of hospitalization/year Oral corticosteroids Long-term oxygen therapy Non-invasive ventilation	3 Years	Death without lung transplant Lung Transplant	0 – 1.5 (low risk) 2 – 3.5 (moderate risk) ≥ 4 (highest risk)

Table 2

Validation of Prognostic Models Reviewed

First Author	Model Validation	Description
Aaron	Internal	80% of sample randomly placed into subsample and 20% into a validation subsample for comparison of agreement between estimated and actual survival
Buzzetti	Internal	The sample was divided randomly and one group developed the prediction model that was tested on the validation group
Liou	Internal	Odd-numbered patients were compared with even numbered patients using logistic regression
Mayer-Hamblett	Internal	10% of the sample became the validation cohort to be compared utilizing logistic regression
McCarthy	External	Mean scores of subgroups compared by outcomes, Histograms of distributions, & ROC curve analysis
Nkam	Internal	A 10-fold cross-validation of the initial data set divided into 10 subsets & fitted onto the other 9 and rotated & repeated 10 times

Table 3

Calculation of the CF-ABLE Score (McCarthy et al., 2013)

CF-ABLE Score	Points
Average FEV_1 for last 3 months is ≥ 52.8	0
Average FEV_1 for last 3 months is < 52.8	3.5
No. of Exacerbations needing IV Antibiotics in last 3 months ≤ 1	0
No. of Exacerbations needing IV Antibiotics in last 3 months > 1	1.5
BMI ≥ 20.1	0
BMI < 20.1	1
Age ≥ 24	0
Age < 24	1
Total Score: 0 – 7 Points	

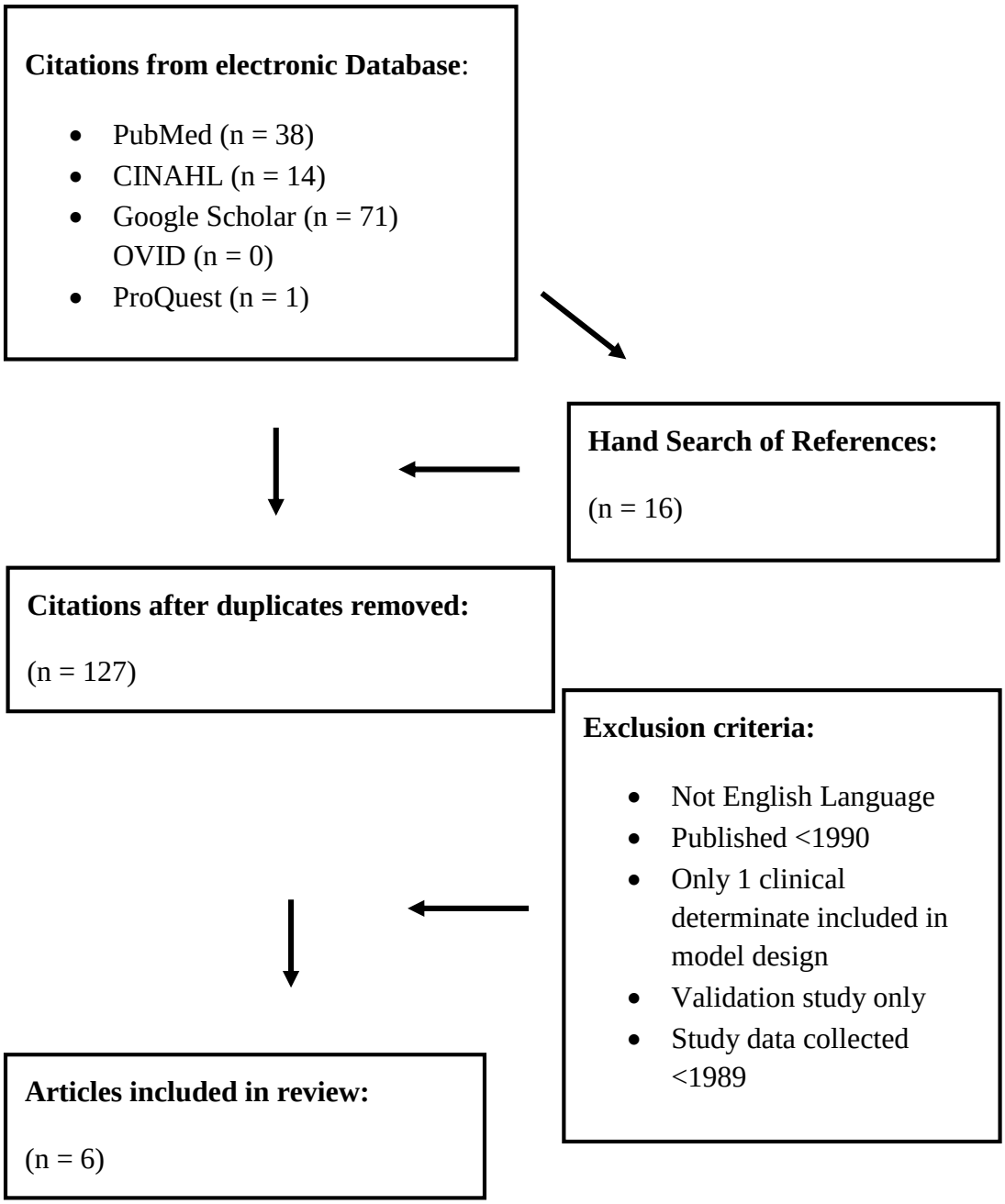

Figure 2. Search strategy

CHAPTER III: SELF-MANAGEMENT BEHAVIORS AND HEALTH OUTCOMES AMONG ADULTS LIVING WITH CYSTIC FIBROSIS

Chapter III is a manuscript describing the findings of a longitudinal, descriptive repeated measures study exploring improved health outcomes among adults living with cystic fibrosis who reported adherent self-management behaviors regarding their prescribed treatment plan. The manuscript is planned for submission to *Journal of Cystic Fibrosis,* or *Chronic Illness*.

Abstract

Modern advances in research and treatment have resulted in an increased number of adults living with cystic fibrosis (CF), but with shortened life expectancy and high treatment burden. An aging CF population requires daily adherence to an arduous prescribed treatment plan. Despite critical importance for health outcomes, there is a lack of research focusing on self-management by adults with CF using a prescribed treatment plan. A longitudinal, descriptive repeated measures design was conducted among adults with CF. We used self-report and a novel adult health outcomes measure during three clinic visits (enrollment, 3 and 6 months following enrollment) to ascertain the feasibility of determining if adults who were adherent to a prescribed treatment plan over time had improved health outcomes. Subjects adhered to their maintenance antibiotics, nutrition/digestion, and disease modifying treatments. No significant visit effects or interaction between visits and adherence were identified. However, adherence to all disease modifying treatment did produce a statistically significant difference on health outcomes (p = 0.014), with those who adhere to all disease modifying treatment (M = 0.67, SD = 1.22) scoring lower on health outcomes than those who do not adhere (M = 2.50, SD = 1.93). Health outcomes improved for those participants in our study who adhered to their disease modifying treatments, showing a statistically significant reduction in risk for transplant or death within the next four

years. Additional inquiry into adherence levels and barriers to maintaining adherence among adults with CF is warranted.

Introduction

Physicians diagnose 1,000 new cases of CF each year (Cystic Fibrosis Foundation [CFF], 2016a). This incurable, progressive, multisystem disease harms numerous organs, primarily the pulmonary and digestive systems, complicates many of the body's normal processes, and shortens life expectancy. Until recently, people living with a diagnosis of CF rarely reached adulthood. Today, over half of the CF patient population are eighteen years of age or older and it is predicted that a person diagnosed with CF has a life expectancy of 40 or more years (CFF, 2016a).

The prescribed treatment plan for CF is highly complex and time consuming requiring two to four hours each day to complete a prescriptive treatment plan (Figure 3). Typically, adults with CF must perform airway clearance, inhale antibiotics or aerosols to dilate airways, thin or clear mucus, utilize inhalers, consume pancreatic enzymes with every meal or snack, incorporate nutritional supplements and vitamins into their diet, ingest oral antibiotics, perform chest physiotherapy, engage in aerobic exercise, and maintain a daily caloric intake sufficient to maintain weight (CFF, 2017; Quick & Byrd-Bredbenner, 2015). In addition, some may be prescribed disease modifying medication if their gene phenotype testing aligns appropriately (CFF, n.d.)

Recommendations are not followed in about 50 percent of those living with CF and is most likely due to challenges with finding up to four hours daily to complete the entire regimen (Elborn, 2016; Latchford, Duff, Quinn, Conway, & Conner, 2009). If they do not implement these recommended tasks several times per day and rid the lungs of excess mucus, people with CF will

increase their likelihood of bacterial growth and colonization, leading to possible pulmonary exacerbation and reduced lung function, health decline, and possibly death (CFF, n.d.).

Medication adherence, or the extent by which a patient takes medications as prescribed (Khanna, Pace, Mahabaleshwarkar, Basak, Datar, & Banahan, 2012) varies in CF and is estimated to range from approximately 35-75% depending on the measure, medication, and population characteristics (Eakin & Reikert, 2013; Tappenden, Sadler, & Wildman, 2017). According to the CFF (2012), nearly one in every five CF patients has reported skipping doses of medication or delaying treatment due to costs. The average annual economic burden for one person's CF treatment is more than $40,000 and due to the rising costs related to recommended treatments and therapies, insurance premiums have increased 20% for people living with CF (CFF, 2012). Maintaining the prescribed level of care can cost an adult living with CF over $300,000 in their lifetime (Rubin, Thayer, Watkins, Wagener, Hodgkins, Schechter, 2017). This high economic and treatment burden prompts the CF healthcare community to work to provide evidence-based treatment and adherence recommendations.

With life-threatening complications associated with the need for adherence, healthcare professionals require insight into which adherence categories are most impactful among adults living with CF. Currently, adherence to treatments in categories such as airway, digestion, disease-modifying, and infection-control are necessary to maintain health (Briesacher, Quittner, Saiman, Sacco, Fouayzi, & Quittell, 2011). Importantly, there is a need for studies investigating a relationship between adherence to prescribed self-management regimes and health outcomes (Tappenden et al, 2017). Limited evidence regarding adherence to treatments as they relate to health outcomes constrains the ability of health professionals to make population sensitive

recommendations. There is minimal research on adherence and health outcomes among adults with CF.

Problem

Adults living with CF now outnumber children in this population and as more reach adulthood, live independently and encounter adult life challenges, recommendation for self-management require change (CFF, 2017). For decades, researchers have focused on children and adolescents with CF, but this childhood disease has progressed into one predominantly of adulthood, with little research focus on adults. An aging CF population requires continuous self-management and adherence to multiple treatments and medications (CFF, 2017). Studies aimed at understanding the impact of adherence to the components of the treatment plan on outcomes of adults self-managing is paramount. Preventing additional societal and economic costs associated with avoidable hospital admissions, morbidity, and mortality among adults living with CF is possible, with the appropriate research and recommendations addressing this population. However, the CF self-management literature lacks an exclusive focus on the adult and the impact of adherence to their prescribed treatment plan on health outcomes..

A documented understanding regarding self-management of the overall prescribed treatment plan and impact to health outcomes among adults living with CF does not exist. Researchers have explored the experience of living with and managing CF for children (Dashiff, Suzuki-Crumly, Kracke, Britton, Moreland, 2013; Goodfellow, Hawwa, Reid, Horne, Sheilds, McElnay, 2015; Jamieson, Fitzgerald, Singh-Grewal, Hanson, Craig, & Tong, 2014); adolescents and young adults transitioning from having assistance with their prescribed treatment plan to self-management (Al-Yateem, 2012; Tierney, Deaton, Jones, Oxley, Biesty, & Kirk, 2013); the experience of CF patient siblings (Havermans et al., 2011); as well as parents and caregivers of

CF patients (Barker & Quittner, 2016; Goodfellow et al., 2015; Sawicki, Heller, Demars, & Robinson, 2015).

Efforts to quantify necessary adherence within the self-management regime may facilitate development of more manageable, patient-centered prescribed treatment plans, improve upon self-management behaviors, and influence health outcomes among adults with CF. We explored the feasibility of identifying categorical adherence and health outcomes among adults with CF when utilizing self-report and a novel health outcome measure. The purpose of this study was to examine the relationship between specific adherence behavior and health outcomes over time; this may enable health professionals to promote adherence considering the unique nature of the self-management experience among adults living with CF.

Research Questions

We hypothesized adherence over time to a prescribed treatment plan would result in better health related outcomes among adults living with CF. The following research questions were addressed:

1. What was the change in health outcomes over visits: (enrollment, 3 months following enrollment, 6 months following enrollment)?
2. What is the difference in health outcomes based on adherence to prescribed treatment categories:
    - all disease modifying (targeted CF protein treatments acting at cellular level);
    - all nutrition/digestion-aid (pancreatic enzymes, diet, supplements, vitamins);
    - all maintenance antibiotics (oral and inhaled antibiotics)?
3. Did health outcomes differ by the interaction between visits and adherence to prescribed treatment categories?

Literature Review

Effective treatments have been developed and contributed to the extensions of life for tens of thousands of people diagnosed with CF, however, patients are not fully participating in their prescribed care. The following is a brief overview of self-management and adherence to provide insight into the challenges faced within the CF population.

Self-Management

In the context of chronic illness, self-management refers to the attitudes and activities individuals adopt to maintain wellness, control symptoms, and prevent acute and chronic complications (Richard & Shea, 2011). Self-management has been linked to improved health status, increased quality of life, continued independence, and decreased medical costs (Flanagan, Damery, & Combes, 2017; Kash, Lin, Baek, & Ohsfeldt, 2017).

For a person with CF, aggressive and arduous CF treatments are required daily, and self-management behaviors may include performing chest physiotherapy, use of airway clearance devices, taking prescribed medications, monitoring respiratory and nutritional status, implementing infection control measures, care for anxiety and depression, and boosting calories to 110% to 220% of the recommended daily allowance (CFF, n.d.; Quick & Byrd-Bredbenner, 2015; Quittner et al., 2012). New approaches to medication and therapeutic treatment, such as innovative drug trials for gene and molecular therapies, are emerging and adding to an already burdensome health maintenance regime (Elborn, 2016). These innovative treatments will require time consuming lab testing processes and arduous navigation of forms required for insurance approvals and payment coverages, as well as additions to the care team, such as a research team; this may lead to increased visit time or number of visits in an already complex multidisciplinary visit schedule (Elborn, 2016; Inacio, 2017).

Adherence

Adherence is a necessary component in self-management of CF. The impact of adherence among those with CF has been attributed to significant variation in patient outcomes (Hebestreit et al., 2018; Knudsen et al., 2016; Zemanick et al., 2010). Researchers indicate poor self-management skill is associated with pulmonary exacerbation and lower baseline lung function (Eakin, Bilderback, Boyle, Mogayzel, & Riekert, 2011; Eakin & Reikert, 2013; Tappenden et al., 2017). Studies in adherence among adults with CF suggest similar rates as other chronic diagnoses (Lin, Kendrick, Wilcox, & Quon, 2017; Sawicki, Sellers, & Robinson, 2009). However, adults living with CF require adherence to a varied and complex daily regime, frequent follow up visits with multiple health specialists, and constant self-monitoring, which makes multiple-adherent behaviors necessary for better health outcomes.

Researchers report lower baseline lung function (Eakin et al., 2011), higher costs (Nasr, Chou, Villa, Chang, & Broder, 2013), and increased hospitalizations (Briesacher et al, 2011) are associated with poor adherence to CF medications. In one study, investigators (Eakin et al, 2011) enrolled CF patients six years of age and older and reported poor adherence to nebulized medication was a significant predictor of having a pulmonary exacerbation requiring intravenous (IV) antibiotic therapy. Historically, adherence researchers limited their studies to one medication or therapy and included children and adolescents, in addition to adults in samples.

The majority of CF patients are facing life challenges that are different than those of the child and adolescent and without an emphasis on the adult living with CF, researchers will be unable to account for their needs. Researchers must capture the lived experience of aging with CF in study design and prepare for subjects that are primarily self-managing their disease. Today's researchers should postulate psychosocial and time factors playing a role in adherence

among adults with CF (Lin et al., 2017). Despite the decades of exposure to the same prescribed treatment plan typical of childhood diagnosis, the adherence levels among adults with CF are low and similar to others with chronic illness (Quittner et al, 2014; Reikert, 2009).

Theoretical Framework

The multifactorial causes of variability in outcomes model (Zemanick et al., 2010) guided this feasibility study (Figure 4). The current model was modified from Schechter's (2003) original introduction and connects the known constructs that may be acting on outcomes among adults living with CF. The causes of variability model (Zemanick et al., 2010) is specific to CF and identifies factors that are consistent with known research regarding management, modifiable and non-modifiable variables, as well as, known outcomes among adult CF patients. The model includes multiple variables within the spheres of genetic factors, medical treatments, and environmental exposures. Each sphere of the model was useful in the selection of measures and informing on variables pertinent to adherence and outcomes research among adults with CF. Within the sphere of medical treatments, Zemanick and colleagues (2010) identified that adherence may be influencing outcomes. Too little available research makes it difficult to establish the exact amount of adherence needed to attain health benefits in this population (Reikert, 2009). Longitudinal studies are needed to better measure the degree to which varying adherence patterns affect health outcomes and whether the strength of associations differ by subgroups among those living with CF (Jennings, Riekert, & Boyle, 2014). The adult CF community lacks adult-sensitive research exploring the existence of relationships between the spheres outlined by Zemanick and colleagues (2010) and also quantifying overall adherence influencing health outcomes.

Zemanick and colleagues (2010) stressed that understanding the influence of self-management behaviors upon outcomes is a critically important task to advancing CF care. Therefore, we believe the multifactorial causes of variability in outcomes model (2010) to be a useful framework to guide research regarding self-management behavior, such as adherence, among adults living with CF.

Methods

Design, Setting, and Sample

This feasibility study used a descriptive, longitudinal repeated-measures design. We obtained approval from both the University and the healthcare institutional review boards. A convenience sample of 18 participants was recruited from a clinic providing healthcare services to a minimum of 50 adults with CF. Inclusion criteria were participants: with a diagnosis of CF made at least one year prior to study entry, ≥18 years of age, and were current patients of a Midwestern adult CF clinic accredited by the National CF Foundation (CFF). Exclusion criteria were participants who had a documented cognitive or physical impairment prohibiting them from completing the research instruments independently or those who were unable to understand the written and/or spoken English language.

Measures

Demographic and other data. We collected health measurements and demographic data from the electronic medical record or EMR as well as prescribed medications and treatments. This information was utilized to describe our subjects, calculate health outcome scores, and determine adherence. Table 4 outlines a list of theoretical and operational definitions of the information collected.

CF-ABLE score. A change in health outcomes in this study was identified by CF-ABLE scores (McCarthy, Dimitrov, Meurling, Gunaratnam, & McElvaney, 2013). Health outcomes scores were calculated from the sum of the individual component scores and were determined by the following: ABLE score [0.0-7.0] = FEV1 % predicted (mean previous 3 months) [0.0-3.5] + number exacerbations (previous 3 months) [0.0-1.5] + age at time of assessment x BMI [0.0-2.0] as identified by McCarthy and colleagues (2013, p.1362).

The CF-ABLE score (McCarthy, 2013) utilizes clinical parameters designated 'ABLE', [age (A), body mass index or BMI (B), lung function (L) expressed as forced expiratory volume in one second (FEV_1), and number of pulmonary exacerbations (E) in the previous 3 months], to predict health outcomes among patients with CF (Table 5). Specifically, the score is a prognostic indicator, which assists clinicians with predicting risk of death or lung transplant within four years, as validated during a five-year period utilizing 370 patients from the national CF Registry of Ireland (CFRI). When the researchers applied the CF-ABLE score to the registry data, there was a significant ($p < .001$) difference found between subgroups of good outcomes ($M = 2.61$, SD = 2.15) and poor outcomes ($M = 5.21$, SD = 1.30); discriminative performance was confirmed by ROC curve analysis (95% CI, 0.77 - 0.88). The researchers validated that the logistic regression model was accurate at predicting death or transplant within the studied cohort.

On average, McCarthy et al. (2013) found a 1-point increase of the CF-ABLE score would lead to an 81% increase in risk of poor outcome within four years (OR, 1.81; 95% CI, 1.46-2.22). The variables included were identified as the best model after a number of them (including gender and genotype) were correlated as potential predictors of death or lung transplant. Each variable's cut-off levels were identified utilizing statistical analysis and/or clinical judgment and then were used to create parameters for "high-risk" (score 5 – 7) and "low-

risk" (score < 2). The resulting score is simple, applicable, and better predicts outcome than FEV_1 alone (McCarthy et al., 2013). The researchers further incorporated the clinical application of the score over two years following development and reported the tool to be useful and concisely predictive of patient prognosis among their subjects (Meurling, McCarthy, Gunaratnam, & McElvaney, 2014). To date, no other studies have been located which utilized the CF-ABLE.

Treatment adherence questionnaire for cystic fibrosis. Inclusion of self-report measures of adherence are cost effective and comprehensive with all aspects of the management regimen, many of which cannot be measured objectively; they also can assess adherence over longer periods of time (Quittner et al, 2014). The use of self-report measures for the study of adherence rates consistently demonstrate high specificity in that patient reports of non-adherent behaviors are valid (George et al., 2010; Quittner et al., 2014).

Figures 5 and 6 identify the Treatment Adherence Questionnaire for CF, or TAQ-CF (Quittner, Espelage, Ievers-Landis, & Drotar, 2000; Quittner et al., 2012), which has replaced both the Disease Management Interview-CF, or DMI-CF (Quittner et al., 2000), and the Treatment Adherence Rating Scale, or TARS (DeLambo, Ievers-Landis, Drotar, & Quittner, 2004). The TAQ-CF does not require specialized training to administer and comprehensively addresses components of the treatment regimen for CF, which is particularly important as treatment may vary across CF centers and physicians (Quittner et al., 2000; Quittner et al., 2012). The TAQ-CF is a brief, self-report questionnaire concentrated on twelve of the prescribed treatments specific for CF and asks subjects to recall and document their frequency, duration, and barriers for each treatment during the previous week.

Efforts to improve the quality of documented adherence behavior includes application of nonjudgmental language in the instructions for the respondents utilizing the TAQ-CF, which normalized the possibility of missed treatments by stating, "*You're not alone if you've missed medications or treatments. It is hard to fit it all in everyday"* (Quittner, Modi, Lamanek, Ievers-Landis, & Rapoff, 2008). Nonjudgmental language facilitates more honest and accurate responses (Rapoff, 2003). Prior studies demonstrated agreement between parents and teens on the TAQ-CF was moderate to high (r =.55 for aerosol medications, r =.78 for CPT), and test-retest reliabilities over one year ranged from .62 to .73 for adolescent reports and .76 to .88 for parent reports (DiGirolamo, Quittner, Ackerman, & Stevens, 1997; Quittner et al., 1996). To date, no studies have been located utilizing the TAQ-CF with an adult sample, so a slight modification replacing 'teens' with 'adults' in the questionnaire directions' statement was necessary.

From subjects' report on the TAQ-CF, we identified adherence behavior, specific to the prescribed treatment plan and determined overall adherence by treatment including all disease modifying (targeted CF protein treatments acting at cellular level), all nutrition/digestion-aid (pancreatic enzymes, diet, supplements, vitamins), all maintenance antibiotics (oral and inhaled antibiotics), all airway-related treatment (inhaled, clearance device), and overall prescribed treatment. Of the five treatment adherence categories, none of the subjects adhered to overall prescribed treatment and all airway-related treatment, resulting in no further analysis.

Procedure

After consenting subjects, they each filled out a set of paper questionnaires. Each participant had their own new writing utensil at each data collection point to avoid cross-contamination. Data was collected at enrollment, and then three months and six months post

enrollment. This data collection aligned with recommended CF clinic visit scheduling (CFF, 2016a) and is the typical amount of time an average adult living with CF, should be self-managing prior to clinical contact with their health provider. This time frame also allowed for calculation of a health outcomes score using our measure, which required three months of clinical data. We could then explore for the interaction between adherence to treatment over time and health outcomes within our sample.

Data Analysis

All calculations and summary statistics to describe the sample characteristics were done in IBM Statistical Package of the Social Sciences (SPSS) 22.0 (IBM Corp, Armonk, NY, 2013). The small sample size of 16 adults with CF led to insufficient power and the violation of required normality assumption for the initially proposed within-between repeated-measures ANOVA. As an alternative, an ANOVA-type statistics using "nparLD" package (Noguchi, Gel, Brunner, & Konietschke, 2012) in R was run to test the proposed hypotheses using the Brunner-Langer nonparametric analysis of longitudinal data in factorial experiments. The main and interaction effects between overall adherence by treatment category and time on health outcome scores were examined. Bonferroni's adjustment for Type I error was applied due to multiple testing so all statistical significances were reported at $p \leq 0.015$.

Results

We recruited 18 subjects, 16 completed data collection, with a response rate of 88.9%. One subject did not return for treatment and one died. Our sample characteristics illustrate similarities to adults living with CF today according to a recent CFF Patient Registry Annual Data Report representing nearly 84% of all CF patients in the United States (CFF, 2016b, 2017). Our sample included 62.5% (n = 10) of females, half (50.0%; n = 8) attended or completed

college, 62.5% (n =10) working full/part-time, and 68.8% (n=11) married/living together (Table 6). All subjects had some form of insurance coverage through either an employer or government. Our sample's genotypes included a majority with the most common mutation, homozygous delta F508 (56.3%); this mutation impacts almost 70% of all affected with CF worldwide (Stanford Medicine, 2017). Participants' mean rating on a self-appraised stress questionnaire was high.

Adherence Differences on Health Outcomes

To test differences between adherence groups for CF-able scores over visits, nonparametric within-between repeated measures ANOVAs were run. Further analyses were run on adherence to all disease modifying treatment, adherence to all nutrition/digestion-aid treatment, and adherence to all maintenance antibiotic treatment. Results of the CF-able scores are presented in Table 7 and Table 8.

Health Outcomes Scores by Adherence to All Disease Modifying Treatment

The effect of visits nor the interaction effect between adherence to all disease modifying treatment and visits did not reach statistical significance. However, patients' adherence to all disease modifying treatment did produce a statistically significant difference on CF-able scores ($p = 0.014$), with those who adhere to all disease modifying treatment ($M = 0.67$, $SD = 1.22$) scoring lower than those who do not adhere ($M = 2.50$, $SD = 1.93$).

Health Outcomes Scores by Adherence to All Nutrition/Digestion-aid Treatment

Neither visits nor the interaction between adherence to all nutrition/digestion-aid treatment and visits reached statistical significance. Patients adhering to all nutrition/digestion-aid treatment ($M = 1.75$, $SD = 1.91$) were not found to be significantly different in CF-able scores from those adhering to all nutrition/digestion-aid treatment ($M = 1.95$, $SD = 1.95$).

Health Outcomes Scores by Adherence to All Maintenance Antibiotic Treatment

Like the case in the above two tests, neither visits nor the interaction between adherence to all maintenance antibiotic treatment and visits did not reach the statistical significance. Patients adhering to all maintenance antibiotic treatment (M = 2.29, SD = 1.95) were not found to be significantly different in CF-able scores from those adhering to all maintenance antibiotic treatment (M = 0.33, SD = 0.50).

Discussion

This study explored a relationship between specific adherence behavior and health outcomes over time. We hypothesized adherence over time to a prescribed treatment plan would result in improved health related outcomes among adults living with CF. We also explored the feasibility of identifying categorical adherence [all disease modifying (targeted CF protein treatments acting at cellular level); all nutrition/digestion-aid (pancreatic enzymes, diet, supplements, vitamins); all maintenance antibiotics (oral and inhaled antibiotics)] and health outcomes among adults with CF when utilizing self-report and a health outcome measure.

Our sample included subjects with a documented modifier gene (37.6 %); researchers are reporting that variability in disease severity and outcomes are likely influenced by modifier genes (Inacio, 2017; Vanscoy et al., 2007). It is noteworthy to mention efforts to study and document modifier genes among CF patients is underway to better understand the pathophysiology and progression of outcomes (Inacio, 2017). Disease modifying treatments are promising, as revealed in the study results. Health outcomes improved for those participants in our study who adhered to their disease modifying treatments, showing a statistically significant reduction in risk for transplant or death within the next four years. Additional inquiry into adherence levels and barriers to maintaining adherence among adults with CF is warranted,

which may enable health professionals to promote adherence while taking into account the self-management experience for adults.

Efforts to recognize the complexity of managing absolute adherence to the prescribed treatment regime overall while meeting the expectations of adulthood, such as independence, employment, financial responsibility, social-wellbeing, navigation of the healthcare system, and having a family of their own, should be considered among this population. Although insurance coverage assures some form of assistance was available for all of our subjects, the existence of barriers to access and limited availability of care, medications, reimbursement, and durable medical equipment outlined by their carriers is well documented (Kraft, 2012; Lyon, Douglas, & Cooke 2014). The Perceived Stress Scale (PSS) results indicated higher stress levels among our sample than those found in the national norm group sample taken from over 2,400 U. S. respondents (Cohen, Kamarck, & Mermelstein, 1983; Cohen & Williamson, 1988). Higher levels on the PSS suggest the respondent's self-perception of how unpredictable, uncontrollable, and overloaded they have found their life over the previous month and have been associated with difficulty self-managing chronic disease (Cohen et al., 1983). The introduction of individualized adherence expectations may assist with motivation and self-efficacy to adhere.

In this study, participants' adherence to all nutrition/digestion-aid and maintenance antibiotics treatment had a non-significant relationship with health outcomes. It has been established that proper nutrition influences lung function; in addition, BMI and lung exacerbation are associated with mortality risk among CF patients (CFF, 2017; Courtney et al., 2007; de Boer, et al., 2011; Fogarty, Britton, Clayton, & Smyth, 2012; Sanders, Bittner, Rosenfeld, Redding, & Goss, 2011). Obtaining a larger sample size is needed for future research. Further research could help support identification of a therapeutic individualized rate of

adherence by treatment category and adherence pattern which may be more manageable for adults living with CF and lead to improved quantity and quality of life.

Implications for Future Research

Repeating the study across different CF clinics to obtain a large sample and including patients who are not under the care of a CF specialist, but are managed primarily by a pulmonologist or general practitioner, may provide variability and capture patients not diagnosed early in life. Future researchers may benefit from attempting to enroll patients identified as self-managing well and not self-managing well by the CF clinic staff. Continuing to collect data, even when subjects are admitted to inpatient settings during exacerbation, or enrolling based upon a baseline health outcomes or prognostics scores to ensure a more representative sample of the population may also decrease threats to external validity. Including objective measures of adherence data, such as pill count devices, or pharmacy refill data is may lead to more reliable data collection in future studies. Also, identifying subjects' knowledge regarding their prescribed treatment plan and the importance of adherence in relation to their health outcomes may provide needed insight into barriers not captured on the tools utilized in the current study.

There is a need for future adult CF research to target development and refinement of adherence tools. A gold standard for adherence measurement is nonexistent and difficulty in obtaining adherence measures is well documented (Jennings et al., 2014; van den Boogaard, Lyimo, Boeree, Kibiki, & Aarnoutse, 2011). Objective measures of adherence can be expensive and insensitive to fluctuations in the variable adherence patterns of those self-managing CF (Quittner et al., 2014) but can be desirable for limiting bias found with some self-report measures. Patient health literacy and self-efficacy and their impact on adherence are important factors to consider (Quittner et al., 2008). Our study collected information regarding current

stress levels experienced by subjects and barriers to adherence, including access. Smith and colleagues (2010) reported emotional symptoms had a significant impact on adherence, therefore, incorporating impact from stress and situations that can increase stress, such as healthcare access, on adherence discussions with adults could assist with tailoring intervention strategies.

Strengths

Socio-demographic characteristic data were explored for significant differences among those who participated, in an attempt to increase generalizability to the adult CF population. Accurate, consistent data collection by one researcher contributed to the internal validity of the study. Well-established measures were selected with reported psychometric properties and validity data. The CF-ABLE and TAQ-CF questionnaire, both novel to use with adults living with CF in the United States were utilized, broadening the tools' exposure to the adult CF healthcare community.

Limitations

Several limitations of the study are worth mentioning. First, data were collected in a single clinical outpatient setting with a small sample of patients. There was potential for response bias due to the convenience sample. Patients who were not feeling well may have not been motivated to participate and further reduced generalizability. Also, the self-report measure relied on accurate recall of information by the subject over time and this could have contributed to problems with external validity. Individuals who missed clinic appointments or were hospitalized were unavailable to enroll in the study and could have contributed to greater variability of health outcomes. Concerns regarding internal validity include level of nonresponse and discontinuing the study.

Conclusion

Ideally, future adult CF adherence research benefits include both participants and the CF healthcare community. Subjects who complete detailed survey tools could become acutely aware of successful self-management behaviors and have the potential to engage in dialogue regarding these expectations with their interdisciplinary teams. These teams have the capability of assisting to deepen health literacy, identify barriers, and encourage adherence behaviors among their adult patients. In our study, adherence in one area of a treatment plan produced a statistically significant change in health outcomes using a prognostic health indicator among a small sample. This finding could be helpful to clinicians and patients by highlighting that there are indications to explore the health outcomes potential of adherence to specific areas of CF treatment plans over others, thus altering the daily burden of current treatment plans from 100% compliance in all treatment areas to more variable adherence patterns.

Current adult CF treatment plans are burdensome and lack insight into the potential of specific adherence patterns. Additional research with a focus on the adult CF population may be useful to researchers and clinicians to evaluate health outcomes in the clinic setting, construct individualized, patient-centric treatment recommendations that account for current evidence and patient genetic testing. Research results may further aid health care professionals to promote and facilitate specific adherence levels among the adult CF population. The potential exists to improve the quality of life and health outcomes for this vulnerable population.

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Table 4

Theoretical and Operational Definitions of Key Demographic Variables EMR Review

Variable Name	Definition	Measure	Type
CFTR *(Cystic Fibrosis Transmembrane Conductance Regulator)*	Dysfunctional protein in CF patients	CFTR genotype variation	Categorical
Modifier genes	Genetic variants responsible for complications of CF	Expression of modifier genes	Categorical
Gender	Biological expression	Self-report as Male or Female	Categorical
Microorganisms	Invading organism in the lungs	Presence in sputum culture (Pseudomonas, MRSA, or other)	Categorical
Tobacco Smoke	Exposure to tobacco smoke	Smoker, Non-smoker, Lives with a smoker	Categorical
Nutrition	Body fat indication based upon weight & height	Calculated utilizing BMI *(Body Mass Index)*	Continuous
Stress	Current level of stress experienced	Perceived Stress Scale (PSS) questionnaire	Continuous
Age	# of years since birth	Date of Birth	Continuous
Age at Diagnosis	Date of confirmed CF diagnosis	Age at time of diagnosis	Continuous
CF Diagnosis Confirmation	Diagnostic laboratory testing	Dysfunction of CFTR (gene analysis), sweat test	Continuous
Prescribed Care	Prescribed management behaviors, medications & treatments	Prescribed Treatment Plan (PTP) as recommended by the CFF	Categorical
Adherence	Frequency patient engages in prescribed behaviors, treatments, or medications	TAQ-CF questionnaire	Continuous
FEV_1 *(Forced Expiratory Volume in 1 second)*	Measure of lung function	Spirometer measurement	Continuous
Exacerbations	Symptomology requiring IV antibiotics	# in previous 3 months	Continuous
Insurance Status	Ability for timely use of personal health services	Medicaid, private insurance, no insurance	Categorical

Table 5

Calculation of the CF-ABLE Score (McCarthy et al., 2013)

CF-ABLE Score	Points
Average FEV_1 for last 3 months is ≥ 52.8	0
Average FEV_1 for last 3 months is < 52.8	3.5
No. of Exacerbations needing IV Antibiotics in last 3 months ≤ 1	0
No. of Exacerbations needing IV Antibiotics in last 3 months > 1	1.5
BMI ≥ 20.1	0
BMI < 20.1	1
Age ≥ 24	0
Age < 24	1
Total Score: 0 – 7 Points	

Note. Used with permission.

Table 6

Characteristics of the Sample (n = 16)

Characteristic	*n* (%)	*M* (*SD*)
Age (at time of enrollment)		*30.3 (8.6)*
Age at Diagnosis		*2.9 (5.4)*
Gender		
Male	6 (37.5)	
Female	10 (62.5)	
Highest Education		
High school/GED	5 (31.3)	
Some college	2 (12.5)	
Bachelor's degree	5 (31.2)	
Master's degree	1 (6.3)	
Other	3 (18.7)	
Work Status		
Full-time	8 (50.0)	
Part time	2 (12.5)	
Disabled	4 (25.0)	
Unemployed	2 (12.5)	
Gross Annual Earnings		
Less than $25,000	5 (31.3)	
$25,000 to $49,999	2 (12.5)	
$50,000 to $74,999	4 (25.0)	
$75,000 to $99,999	4 (25.0)	
$150,000 or more	1 (6.3)	
Marital Status		
Married	10 (62.5)	
Single	5 (31.3)	
Living together	1 (6.3)	
Insurance		
Private/employer	11 (68.8)	
Government	5 (31.2)	
Genotype		
Heterozygous delta F508	7 (43.8)	
Homozygous delta F508	9 (56.3)	
Modifier gene identified	6 (37.5)	
Perceived Stress Scale score (PSS)		***20.5 (3.7)***

Note. *M* = Mean; *SD* = Standard deviation; PSS (Cohen, Kamarck, & Mermelstein, 1983)

Table 7

Descriptive Statistics for CF-ABLE Health Outcomes Score at Each Data Collection

	Adherence					
	No			Yes		
	Visit 1	Visit 2	Visit 3	Visit 1	Visit 2	Visit 3
	M +/- SD	*M* +/- SD	*M* +/- SD	*M* +/- SD	*M* +/- SD	*M* +/- SD
Disease modifying treatments	2.36 +/- 1.95	2.77 +/- 2.05	2.36 +/- 1.95	0.90 +/- 1.51	0.90 +/- 1.51	0.20 +/-0.45
Nutrition / digestion-aid treatments	1.93 +/- 1.93	2.25 +/- 2.09	1.67+/- 1.93	1.75 +/- 2.47	1.75 +/- 2.47	1.75 +/- 2.47
Maintenance antibiotic treatments	2.27 +/- 1.93	2.62 +/- 2.04	2.00 +/- 1.98	0.33 +/- 0.57	0.33 +/- 0.57	0.33 +/-0.57

Note. *M* = Mean; *SD* = Standard deviation

Table 8

Effects of Adherence, Time, and Their Interaction on Health Outcomes

Treatment Category	Statistic	Df	*P* value
Disease modifying treatments			
Adherence (No vs. Yes)	5.94	1	0.014*
Visit (Visit 1 – Visit 3)	4.07	2	0.131
Adherence × Visit	2.16	2	0.339
Nutrition/digestion-aid treatments			
Adherence (No vs. Yes)	0.10	1	0.753
Visit (Visit 1 – Visit 3)	5.18	2	0.075
Adherence × Visit	5.18	2	0.075
Maintenance antibiotic treatments			
Adherence (No vs. Yes)	4.58	1	0.032
Visit (Visit 1 – Visit 3)	5.31	2	0.070
Adherence × Visit	5.31	2	0.070

Note. * $p < .015$ using Bonferroni's adjustment for Type I error

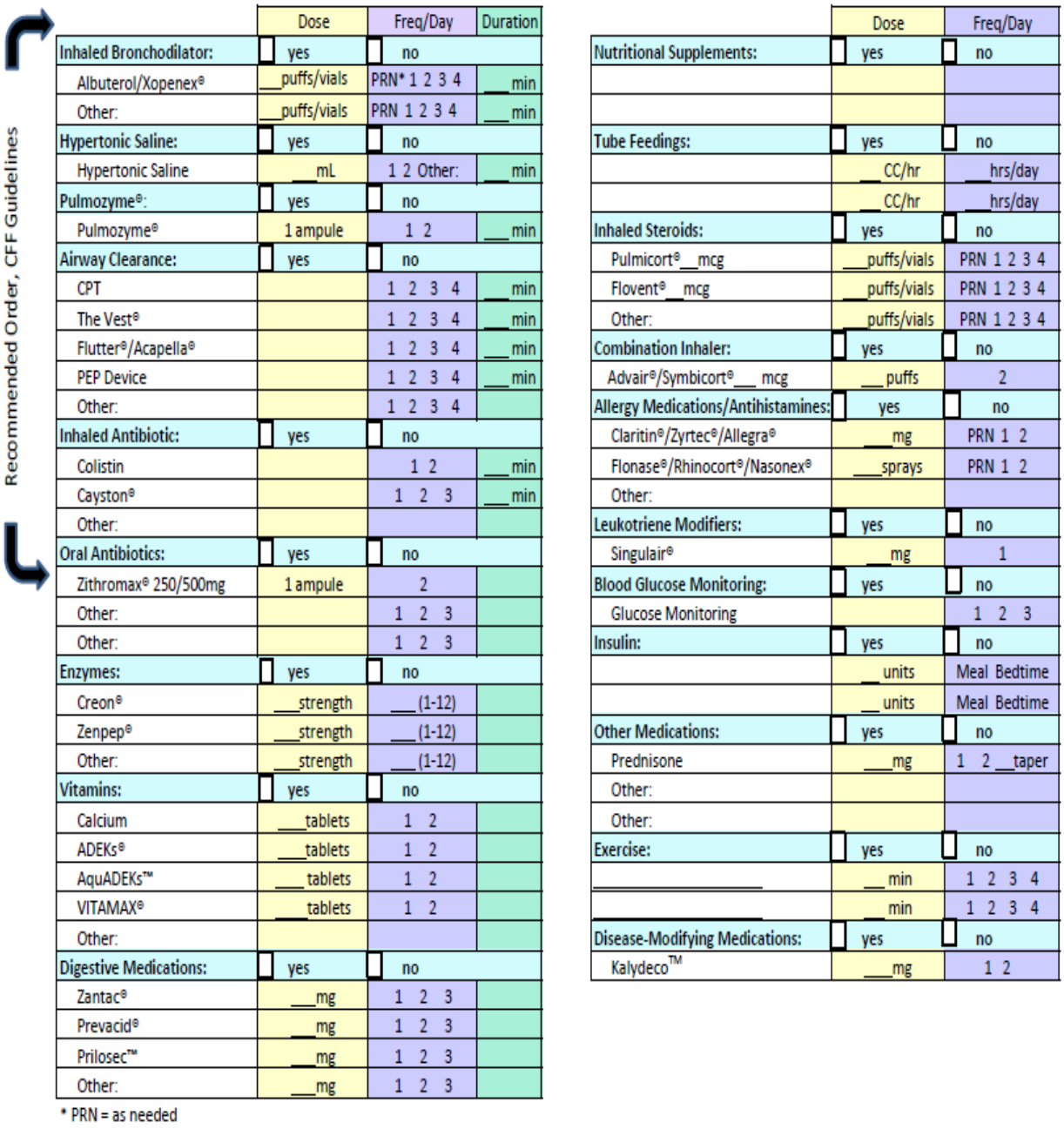

Figure 3. Typical daily adult CF health maintenance requirements and frequency. Prescribed Treatment Plan, by Quittner, A. L., 2000, Retrieved from http://www.psy.miami.edu/ksa_measures/pub.phtml. Copyright [2011] University of Miami. Reprinted with permission.

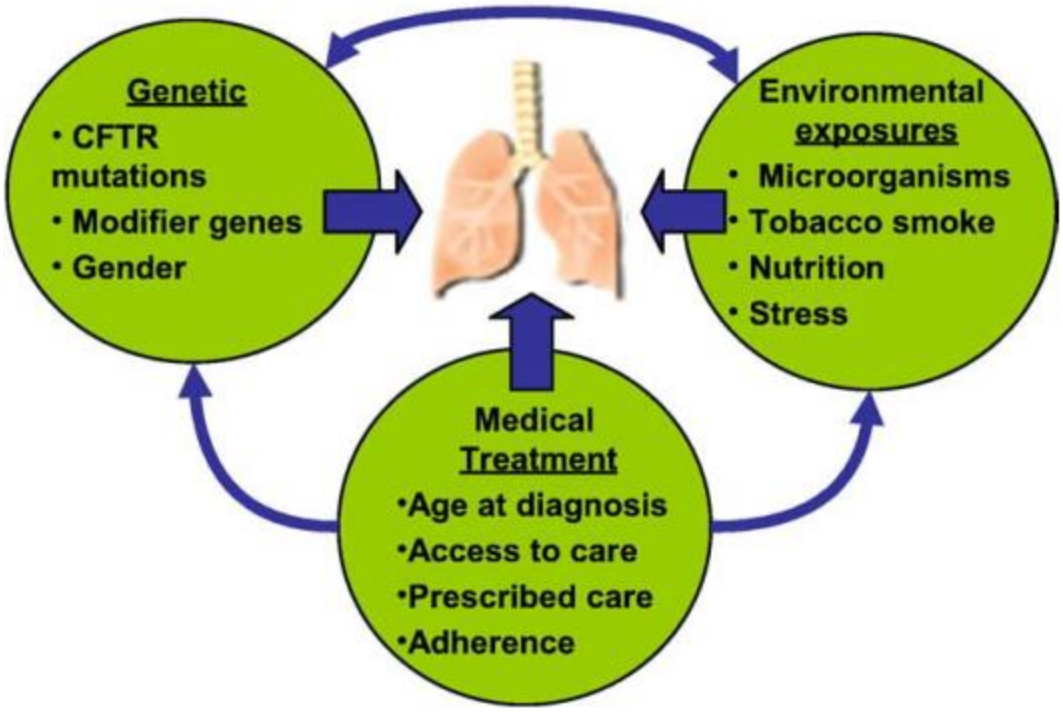

Figure 4. The multifactorial causes of variability in outcomes model (Zemanick et al., 2010) Zemanick and colleagues modified from Schechter's (2003) original introduction. Connects the known constructs that may be acting on health outcomes among a person with CF, including multiple variables within the spheres of genetic factors, medical treatments, and environmental exposures. Used with permission.

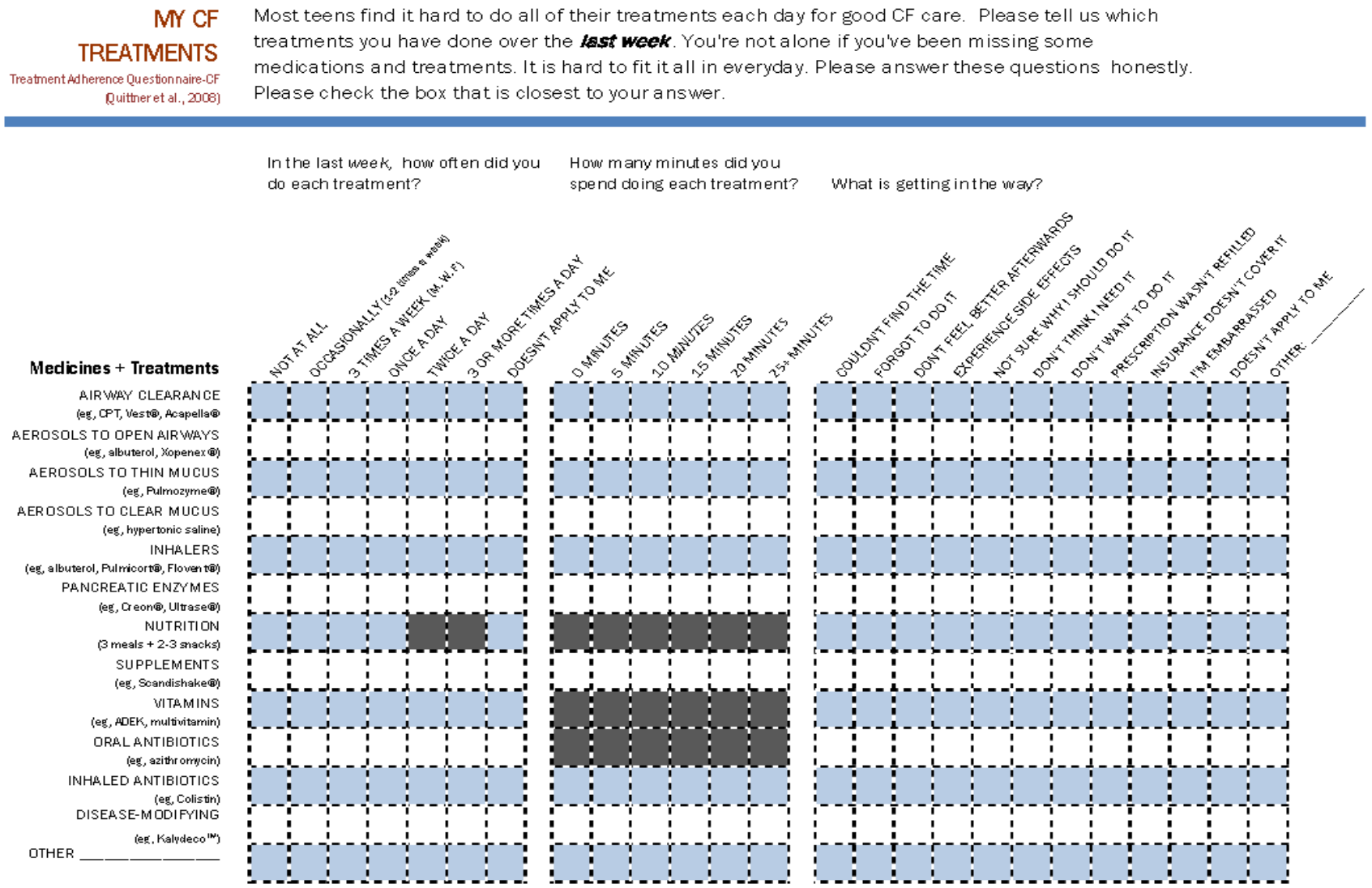

Figure 5. TAQ-CF by Quittner et al., 2008, Retrieved from http://www.psy.miami.edu/ksa_measures/pub.phtml. Copyright [2011] University of Miami. Reprinted with permission.

RESEARCH#

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Most people find it hard to do all of their treatments each day for good CF care. Please tell us which treatments you have done over the ***last week.*** You're not alone if you've been missing some medications and treatments. It is hard to fit it all in everyday. Please answer these questions honestly. Please check the box that is closest to your answer.

Treatment Adhereance Questionnaire-CF
Quittner et al., 2008

In the last week, how often did you do each treatment?

How many minutes did you spend doing each treatment?

What is getting in the way?

Medicines + Treatments	NOT AT ALL	OCCASIONALLY (1-2 times a week)	3 TIMES A WEEK (M,W,F)	ONCE A DAY	TWICE A DAY	3 OR MORE TIMES A DAY	DOESN'T APPLY TO ME	0 MINUTES	5 MINUTES	10 MINUTES	15 MINUTES	20 MINUTES	25+ MINUTES	COULDN'T FIND THE TIME	FORGOT TO DO IT	DON'T FEEL BETTER AFTERWARDS	EXPERIENCE SIDE EFFECTS	NOT SURE WHY I SHOULD DO IT	DON'T THINK I NEED IT	DON'T WANT TO DO IT	PRESCRIPTION WASN'T REFILLED	INSURANCE DOESN'T COVER IT	I'M EMBARRASSED	DOESN'T APPLY TO ME	OTHER:_____
AIRWAY CLEARANCE (CPT, Vest ®, Acapella ®)																									
AEROSOLS TO OPEN AIRWAYS (albuterol, Xopenex ®)																									
AEROSOLS TO THIN MUCUS (Pulmozyme®)																									
AEROSOLS TO CLEAR MUCUS (hypertonic saline)																									
INHALERS (albuterol, Pulmicort®, Flovent®)																									
PANCREATIC ENZYMES (Creon®, Ultrase®)																									
NUTRITION (3 meals + 2-3 snacks)																									
SUPPLEMENTS (Scandishake®)																									
VITAMINS (ADEK, multivitamin)																									
ORAL ANTIBIOTICS (azithromycin)																									
INHALED ANTIBIOTICS (Colistin)																									
DISEASE-MODIFYING (Kalydeco™)																									
OTHER _____																									

Figure 6. TAQ-CF, *modified for adult use with removal of 'teens'*, by Quittner et al., 2008, Retrieved from http://www.psy.miami.edu/ksa_measures/pub.phtml. Copyright [2011] University of Miami. Reprinted with permission.