Chronic Respiratory Therapies in Cystic Fibrosis: Addressing Adherence

In this Issue...

The treatment regimen for people with cystic fibrosis is often complex and time-consuming. As a result, nonadherence to chronic cystic fibrosis (CF) therapies is common and has been linked to poor health outcomes. Barriers to adherence in CF are multifactorial, involving the patient, family, clinician, and health system.

In this issue, Dr. Gregory Sawicki from Boston Children’s Hospital and Harvard Medical School reviews key data describing rates of nonadherence to chronic respiratory therapies in CF (including inhaled antibiotics, chronic respiratory therapies, and novel CFTR modulators), as well as recent research into improving adherence behaviors.

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Identify common barriers to adherence among people with cystic fibrosis.
- Describe how nonadherence in cystic fibrosis can affect health outcomes.
- Discuss strategies to measure and improve adherence among children, adolescents, and adults with cystic fibrosis.

GUEST AUTHOR OF THE MONTH

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Commentary & Reviews

Dr. Gregory Sawicki has disclosed that he served as an advisor for Gilead and as a consultant to Genentech and Vertex.

Unlabeled/Unapproved uses

Dr. Gregory Sawicki has indicated that there will be no references to the unlabeled or unapproved use of any drugs or products.

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COMMENTARY

Adherence to Inhaled Antibiotics vs Health Care Utilization

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Program Directors

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Over the past several decades, health outcomes in cystic fibrosis (CF) have improved across the population, with over 50% of people living with CF in the US now over the age of 18 years. These improvements have been due in part to the development of new therapies including inhaled antibiotics, antiinflammatories, mucolytics, and most recently CFTR modulators. Quality improvement efforts have also led to greater implementation of treatment guidelines across CF care centers. These advances have resulted in a treatment paradigm for CF that focuses on early, aggressive intervention and management of respiratory symptoms with the goal of reducing the frequency of pulmonary exacerbations, improving nutritional status, and reducing the rate of disease progression. As a result, CF treatment complexity rises in childhood and adolescence; adults with CF are often burdened with over two hours of recommended daily therapies as standard of care. It is no wonder, therefore, that adherence to chronic therapies poses an enormous challenge to people with CF, their caregivers, and their health care teams.

Rates of adherence have to routine therapies in CF have frequently been reported as suboptimal. In a single-center study, high levels of nonadherence were associated with lower lung function and higher rates of IV antibiotic therapy. In this newsletter, we review two recent studies that evaluated rates of adherence in national health plan administrative databases. Briesacher and colleagues found that most individuals filled prescriptions for fewer than two courses of inhaled tobramycin over a 12 month period, and a minority had high levels of adherence to inhaled tobramycin. Importantly, those with high levels of adherence to inhaled tobramycin had lower rates of hospitalizations and lower health care costs. Similarly, Quittner and colleagues identified rates of adherence of less than 50% to multiple chronic respiratory therapies, and those with low adherence had more acute care episodes (hospitalizations and emergency department visits) and higher health care costs. Taken together, these papers continue to identify negative health outcomes associated with nonadherence.

A key challenge in addressing nonadherence in CF is accurate measurement of actual adherence behaviors. As demonstrated in the study by Daniels and colleagues, both self-reporting and clinician assessment overestimate adherence when compared to measurements taken from electronically monitored nebulizers. Pharmacy refill data, such as described in the Briesacher and Quittner papers, has advantages over self-reporting, but likely also overestimates adherence, as such data only indicates what medication an individual possesses rather than what they actually administer. Electronic monitors have the potential to provide the most accurate real-time adherence data but are also the most difficult to implement on a wider scale across clinical settings. Nevertheless, as a research tool, electronic monitoring can help identify challenges to adherence and may serve as robust outcome measures for designing interventions.

In the study by Ball and colleagues, adherence to nebulized therapies was monitored over a one-year period in a small group of adolescents with CF. Interestingly, adherence rates were highest during school term weekdays and lowest on weekends and during holiday periods. This study suggests that structured routines may facilitate adherence behavior and thus could be a simple intervention that clinicians could address when discussing treatment regimens with patients and their families.

Although most research on adherence in CF has focused on nebulized therapies,
adherence to other chronic CF medications may also be suboptimal. Ivacaftor, an oral CFTR modulator now available for a small group of people with CF, leads to significant improvements in multiple health outcomes. In a small, yet provocative study led by Siracusa (discussed herein), adherence to ivacaftor as monitored electronically was 61%, similar to rates seen for the more complex nebulized therapies. This study points out that adherence challenges exist not just for medications that are most time-consuming or complex to administer, and interventions should focus on the totality of the CF treatment regimen whenever possible.

Barriers to adherence in CF are numerous and include time pressures, treatment burden, competing priorities, lack of perceived immediate consequences to nonadherence, lack of awareness, willful anger at a chronic disease, and forgetfulness. In the study by Hilliard and colleagues, depression was found to be associated with lower rates of adherence, and this relationship appeared to be mediated by negative beliefs about medication among those who had more depressive symptoms. This study supports a paradigm of mental health screening and intervention that has been recommended in recently published CFF-ECFS mental health guidelines and suggests that mental health interventions could be important in addressing adherence behaviors in CF.

Fundamentally, improving adherence in CF is an essential component of a precision medicine approach to CF care. Despite the body of evidence that alerts the CF community to the prevalence of nonadherence and elucidates the barriers to optimal adherence, there still is a paucity of literature on effective adherence interventions in CF care settings. Further research is needed on improving measurement of adherence, addressing treatment complexity, and designing interventions tailored to individual adherence barriers. Multidisciplinary CF care teams must be at the forefront of such interventions, and research is ongoing exploring the role of technology, problem-solving, motivational interviewing, and cognitive behavioral therapy in addressing nonadherence. Based on such work, successful interventions could be implemented.

References:

Adherence to Inhaled Antibiotics vs Health Care Utilization


Inhaled tobramycin is among the guideline-recommended chronic respiratory therapies for people with cystic fibrosis (CF) who are chronically infected with *Pseudomonas aeruginosa*. In clinical trials, inhaled tobramycin leads to decreased sputum density of *P. aeruginosa* and improved lung function. Long-term use of inhaled tobramycin as documented in the CF Foundation Patient Registry was also associated with decreased mortality. However, rates of adherence to inhaled tobramycin are suboptimal.

In this study, Briesacher and colleagues examined rates of adherence to inhaled tobramycin over five years using a national database of private health insurance claims in the United States. The goals of their study were to describe overall rates of adherence to inhaled tobramycin, as well as to determine whether increased adherence to inhaled tobramycin was associated with decreased health care utilization. To account for the 28 day on-off cycles for inhaled tobramycin prescriptions, the authors developed a measure of adherence calculated as the sum of days supplied of inhaled tobramycin over one year divided by 56. Adherence categories for one year were defined as low utilization (≤ 2 cycles), medium utilization (> 2 to < 4 cycles), and high utilization (≥ 4 cycles). The main measures of health care utilization analyzed were inpatient hospitalizations and overall health care costs, both derived from the administrative claims database.

The authors identified 804 individuals in the database who had CF and prescription claims for inhaled tobramycin during a one year period. Forty-three percent of the individuals were adults. The overwhelming majority (71%) had low utilization of inhaled tobramycin, 22% had medium utilization, and only 7% had high utilization. Rates of utilization did not differ whether a claim for *P. aeruginosa* infection was also identified in the administrative data. Twenty-six percent of those with high utilization had a hospitalization during the year of analysis, whereas 41% of those with medium utilization and 43% of those with low utilization had a hospitalization during the year. Median outpatient costs excluding drug costs were highest for those with low utilization, but median outpatient pharmacy costs were highest among those with high utilization. Using a logistic regression analysis controlling for age, gender, and comorbidities, high utilization was associated with a decreased risk of hospitalization relative to low utilization (adjusted odds ratio (AOR) 0.40; 95% CI 0.19-0.84).

This analysis is the first to directly link utilization of inhaled tobramycin with health care utilization. Overall utilization rates of inhaled tobramycin were low, suggesting that nonadherence to chronic inhaled tobramycin therapy is common. Importantly, those with high utilization were found to have lower rates of hospitalization, providing real-world evidence of the effectiveness of this therapy similar to the efficacy demonstrated in clinical trials. This analysis also provides support to developing interventions that improve adherence to chronic inhaled antibiotic therapy as a means to improve health outcomes for individuals with CF.
Multiple studies have documented low adherence rates to various chronic CF medication. In this analysis, Quittner and colleagues took advantage of a large national administrative claims database to describe adherence rates to multiple commonly prescribed CF medications and to evaluate the relationships between adherence and health care utilization and cost.

For this study, data were obtained from the Thomson Reuters MarketScan Commercial Claims and Encounters Database from January 2005 to June 2011. The database includes medical and drug data for active employees and their dependents with primary coverage through employer-sponsored private health insurance throughout the United States. Patients ≥ 6 years old included in this retrospective cohort study met the following criteria: 1) two or more independent CF diagnoses, 2) one or more prescription fills for a CF pulmonary medication (azithromycin, dornase alfa, hypertonic saline, or an inhaled antibiotic [aztreonam, colistin, or tobramycin]), and 3) continuous enrollment for 180 days. Adherence was calculated as the medication possession ratio (MPR), the cumulative days’ supply of medication dispensed divided by 365 days (excluding hospitalized days). Drug-specific MPRs were calculated for each pulmonary medication and then averaged to obtain a composite MPR (CMPR). CMPR was classified as low (less than 0.5), moderate (0.5 - 0.8), and high (greater than 0.8). Health care utilization outcomes were evaluated over a two-year period. The study included 3,287 patients with CF, with a mean age of 22.8 ± 13.0 years, and 56% were adults. A subgroup of 1,420 patients had continuous eligibility for 730 days and were included in analyses of second-year health care use and cost outcomes.

The mean CMPR in the study sample was 48%; 49% of patients had a CMPR ≥ 0.50, and only 20% of patients had a CMPR ≥ 0.80. Mean MPR was highest for dornase alfa (57%) followed by inhaled tobramycin (51%), chronic azithromycin (50%), inhaled aztreonam (47%), inhaled colistin (42%), and hypertonic saline (40%). The highest rates of adherence were seen in patients ages 6 - 10 years, and the lowest rates of adherence were observed in those aged 18 - 25 and 26 - 35 years. Patients who filled ≥ 1 pulmonary medication had significantly higher adherence than those who filled one medication only (all \( P < .01 \)) (mean CMPR, 41%, 51%, 56%, 60%, and 62% for one, two, three, four, and five medications filled, respectively). In adjusted regression analyses, exhibiting low adherence was associated with significantly more all-cause hospitalizations (OR 1.39, 95% CI 1.19 - 1.62) and all-cause ED visits (OR 1.40, 95% CI 1.14 - 1.73) compared to those with high adherence, with similar results for CF-related hospitalizations and ED visits. There was no association between adherence rates and outpatient visits. Patients with moderate adherence also had higher acute care health care utilization than those with high adherence. These associations persisted into the second year of analysis. In their cost analyses, patients with low and moderate levels of overall adherence were found to be associated with significantly higher health care costs during the first year of analysis, but not during the second year of analysis.

Like other studies looking at adherence to CF medications, this study identified high rates of nonadherence based on pharmacy refills. Lowest adherence was observed in adolescents and young adults, identifying a high-risk group that could be a target for adherence-promotion interventions. The authors also conclude that low adherence was associated with higher health care use and costs, suggesting that interventions targeting improvements in adherence in CF may result in better health outcomes and reduced acute care use.
Adherence to Ivacaftor


Ivacaftor is the first CFTR modulator approved for clinical use in individuals who have CF and a CFTR gating mutation. This oral, twice-daily therapy is the first to target the basic defect causing CF and has led to significant clinical improvements in pivotal clinical trials. In this study, Siracusa and colleagues used data from electronic monitoring and pharmacy refills to examine adherence rates to ivacaftor in a small group of patients.

Eligible patients were approached during routine CF clinic visits. Patients were given an electronic monitoring device (MEMS®) and instructed to use the device to dispense their ivacaftor. MEMS mimics a conventional pill bottle and tracks the date and time of each bottle opening. EM data were used to calculate overall adherence rates, weekly adherence rates, and duration between doses. Self-report measures of medication adherence and pharmacy refill data were also obtained as secondary measures.

Twelve patients enrolled in the study, with a mean age of 20.8 years and mean best FEV₁ 100.7 percent predicted. These patients had been prescribed ivacaftor for an average of 55 weeks (range 11 - 89 weeks). Patients were monitored for an average of 118 ± 35 days. The mean overall adherence rate as measured by the electronic monitor was 61% (range 4% - 99%), and the median duration between doses was 19.8 hours. Adherence rates from pharmacy refills (measured by medication possession ratio) ranged from 13% to 124% with mean (SD) = 84% (31%). With only one exception, self-reported adherence was 100% at both points of measurement during the study. Measured adherence also decreased over time at a rate of - 1.9% per week, and the mean duration of time between doses increased over time. There were no appreciable differences in adherence rates based on lung function or duration of prior ivacaftor therapy.

The authors conclude that adherence rates to ivacaftor are suboptimal and mimic adherence rates found in other studies to other chronic CF medications. In addition to overall adherence measurement, the electronic monitoring method employed in the study identified that duration between doses was prolonged, even among those with better daily adherence. Given the cost of CFTR modulators, the authors also conclude that objective monitoring could help identify nonadherence patterns and allow earlier and individualized intervention to promote adherence to these types of medications.
Depression is one of the many barriers commonly cited for poor adherence among individuals with chronic disease such as CF. Recent epidemiologic data suggest that the rates of depression in CF exceed those of the general population. In this study, Hilliard and colleagues examine the relationship between depression and adherence. In addition, they evaluated medication beliefs as a potential mediator between the relationship between depressive symptoms and adherence behaviors.

This study analyzed baseline data from a single-center cohort of individuals with CF aged 16 and older enrolled in a randomized trial of a motivational interviewing intervention. Depressive symptoms were measured using the Center for Epidemiologic Studies Depression scale (CES–D), with a cutoff score of 16 indicating the presence of elevated symptoms. The research team developed a set of questions to measure four components of medication beliefs, including self-efficacy, motivation, perceived importance, and outcome expectancies as related to CF medications. Data on adherence were obtained from pharmacy refill records and were used to calculate composite medication possession ratios (cMPR).

The study cohort consisted of 128 patients with CF; 53% were male, mean age was 29.2 years, and mean FEV₁ was 63.7 percent predicted. Twenty-three percent of the cohort had elevated symptoms of depression. Average adherence in the cohort was low, with a mean cMPR of 0.44 ± 0.27. Significant bivariate correlations were evident among higher depressive symptoms, more negative medication beliefs, and lower composite adherence rates. There were no significant correlations between depressive symptoms and age or lung function. Having more prescribed pulmonary medications was also significantly correlated with more positive medication beliefs and higher adherence rates.

To evaluate the relationship between depressive symptoms, medication beliefs, and medication adherence, the authors developed a structural equation model to test the hypothesized relationships between the three constructs. In their final analysis, higher depressive symptoms were significantly associated with less positive medication beliefs, and those beliefs were significantly associated with lower medication adherence.

Based on their analysis, the authors conclude that a person’s medication beliefs are one mechanism that may link depressive symptoms and suboptimal adherence in CF. This study suggests several potential points of intervention to improve adherence in CF. One would be to screen for and address depressive symptoms. Additionally, interventions should consider including ways to address a person’s beliefs and perceptions about their prescribed medications as a way to approach adherence promotion.
Differences in Rates of Adherence to Nebulized Therapies Based on Calendar

Ball R, Southern KW, McCormack P, Duff AJ, Brownlee KG, McNamara PS.

Given the complexity of the daily treatment regimen for CF, adherence patterns may vary based on the variation in a person’s daily time pressures. In this study, Ball and colleagues examined adherence data in an observational cohort of adolescents in the UK over a one-year period using retrospective data collected from nebulizers with built-in data logging systems. The primary research question addressed was whether adherence rates differed based on weekday/weekend or school-term/school vacation times.

Data were obtained from 24 patients with CF aged 11 - 17 years followed at two CF centers. All participants had been on chronic respiratory therapies using the Ineb™, an adaptive aerosol delivery device that records the dates and times of treatments. At clinic, the data log was accessed and discussed routinely with individual patients and their families. Over a full scholastic year, the number and dates of all treatments were recorded. Adherence was calculated as the percentage of the number of taken treatments divided by the number of prescribed treatments. All families were aware that their adherence was being regularly monitored.

Fifteen of the 24 participants were prescribed one to two treatments per day. The mean overall adherence was 65% (SD 28%). Mean weekday adherence was significantly greater than that at weekends (weekday, 67%; weekend, 60%; \(P = .001\)). All but three patients had better adherence on weekdays than weekends. Mean term-time adherence was greater than school holiday adherence (term-time, 66%; holiday, 51%; \(P < .001\)) Adherence for 20 of 24 patients was better during term time. There was also a trend for adherence rates to be worst during Christmas time. In this study, patients prescribed one daily nebulized treatment took on average 0.8 treatments/day over the year. Patients prescribed two or three treatments a day had worse daily adherence; on average they took 1.4 treatments a day.

The findings of this study surprised the authors, who had expected that adherence would be better during holidays and weekends; in fact, their data showed the reverse phenomenon. However, their data can be potentially explained by the increased structure and daily family schedule inherent in school days. They conclude adherence interventions should focus on communicating with individual patients about unique time pressures and should emphasize the importance of incorporating treatments into existing daily routines.
Challenges in Assessing Adherence to Nebulized Therapies

Daniels T, Goodacre L, Sutton C, Pollard K, Conway S, Peckham D.

A major challenge to improving adherence behaviors is accurately identifying levels of adherence. Numerous studies have shown that self-reported adherence, including daily diaries, may overestimate adherence. Over the past several years, novel technologies have enabled electronic monitoring of adherence and could be used in obtaining adherence data. In this study, Daniels and colleagues assessed and compared rates of adherence using three methods: self-report, clinician report, and electronic monitoring. The electronic monitor used was the I-neb™, an adaptive aerosol delivery system that can record treatment date, time, and duration.

This was a cross-sectional study of 63 adults with CF (mean age 26 years, mean FEV₁ 55.5 percent predicted) recruited from a single CF care center in the UK. Participants were already using the I-neb as part of routine clinical care. At a clinic visit, they were also asked a series of questions to gather self-report data on adherence levels of the previous three months. In addition, clinicians (physicians, nurses, dietitians, physiotherapists, and pharmacists) were asked to provide a clinician assessment of adherence. The authors calculated bias between self- or clinician- report and I-neb data as their measure for over- or under-estimation. The primary self- and clinician- report question was a variation of “what percentage of nebulizers was taken by the participant over the previous three months?”

In this study, the median adherence level significantly differed based on the modality of measurement. The lowest levels of adherence were identified by the electronic monitor (median 36%) and the highest were identified by self-report (median 80%). Using electronic monitor data, those with higher levels of adherence were older (P = .001) and more likely to be male (P = .044). There was no difference in electronically monitored adherence level based on lung function or number of prescribed nebulized medications.

There was significant overestimation of adherence when measured by both self-report and clinician-report. The overall mean bias of self-report was 25%. Overestimation was most pronounced among those with lower levels of recorded adherence (< 60%). Similarly, clinicians overestimated adherence levels, with bias ranging from 2.3 - 19.1. There was also extreme inaccuracy for individuals. The authors provide two examples: 1) in one participant, adherence downloaded from the I-Net was 109% of prescribed treatment, whereas physiotherapist estimation was 7%; 2) in another participant, the downloaded adherence was 0%, whereas physiotherapist estimation was 71%.

The authors conclude that both self-report and clinician-report overestimate levels of adherence to nebulized medications. They also conclude that no individual clinician’s assessment of patient adherence should influence treatment decisions, as there can be significant overestimation. They suggest that electronic monitoring could be used to provide an accurate long-term record of adherence levels, which may aid the clinician in improving communication and tailoring treatment to an individual.

KEY TAKEAWAYS

- Adherence to chronic CF therapies, including inhaled antibiotics and novel CFTR modulators, is suboptimal.
- Lower rates of adherence to chronic CF therapies are associated with worse health outcomes and increased health care utilization.
- Barriers to adherence in CF include erratic schedules, treatment complexity, and mental health comorbidities, and interventions to identify and address these barriers.
are needed.

IMPORTANT CME/CE INFORMATION

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