JPPT | Retrospective Clinical Investigation

Association of Medication Regimen Complexity With Clinical Endpoints in Pediatric Patients With Cystic Fibrosis

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OBJECTIVE Cystic fibrosis (CF) patients and caregivers are impacted by the number of pharmacological agents and unique administration needs; however, no data currently assesses how medication regimen complexity impacts clinical outcomes in this population. The objective of this study is to evaluate if an association exists between increased medication regimen complexity and clinical endpoints in pediatric patients with CF.

METHODS This retrospective analysis included all pediatric patients with CF (ages 5–20 years) with at least 2 pharmacist encounters and acceptable pulmonary function tests at our pediatric pulmonary clinic during 2017. Each patient's medication regimen was scored using the validated Medication Regimen Complexity Index (MRCI) tool. The primary outcome was the correlation between MRCI score and lung function. Secondary endpoints included growth, number of infections requiring antibiotics, and hospitalizations.

RESULTS MRCI scores of the 113 included patients ranged from 2 to 101 points. A negative correlation was found between initial and final MRCI score and initial and final forced expiratory volume in 1 second (FEV_1; $r = -0.323$, $p = 0.0005$ and $r = -0.287$, $p = 0.0021$, respectively). MRCI scores were negatively correlated with BMI percentile for both encounters ($r = -0.162$ and $r = -0.125$) but were not significant. Higher MRCI scores were associated with increased use of oral and intravenous antibiotics and hospital admissions.

CONCLUSIONS Higher MRCI scores are correlated with a significant decrease in FEV_1, increased need for antibiotic therapy, and more hospital admissions in pediatric patients with CF. Larger studies are needed to determine if a correlation exists between MRCI score and growth.

ABBREVIATIONS BMI, body mass index; CF, cystic fibrosis; CFTR, Cystic fibrosis transmembrane conductance regulator; FEV_1, forced expiratory volume in 1 second; HIV, human immunodeficiency virus; IV, intravenous; MRCI, Medication Regimen Complexity Index; UNC, University of North Carolina

KEYWORDS ambulatory care; cystic fibrosis; medication adherence; medication regimen complexity; pharmacists; polypharmacy; treatment outcome

J Pediatr Pharmacol Ther 2021;26(3):248–252

DOI: 10.5863/1551-6776-26.3.248

Introduction

Cystic fibrosis (CF) is an autosomal recessive disease characterized by chronic, progressive, obstructive lung disease further complicated by multisystem manifestations in the sinuses, liver, pancreas, and intestine.[1] Approximately 30,000 individuals are affected with CF in North America, and the predicted median survival is 44 years for people living with CF who were born between 2013 and 2017.[2] Patients living with this chronic disease deal with costly, time-consuming, and burdensome medication therapies on a daily basis. On average, patients with CF use 8 to 10 medications daily, total administration time can take 1 to 3 hours each day, and average monthly copayments can range from $107 to $310.[3] These challenges contribute to estimated nonadherence rates of 20% to 70% in this population.[4]

Patients with CF typically share a similar pharmacotherapy backbone; however, these regimens change both acutely and longitudinally due to age, adverse effects, colonization, infection, and disease progression. As complexity increases, this can lead to difficulties with adherence, medication access, adverse effects, and drug interactions, which may potentially precipitate poor clinical outcomes. All these areas can be directly impacted by a dedicated CF clinical pharmacist. In 2017, the University of North Carolina (UNC) Pediatric Cystic Fibrosis Center cared for 335 patients. Patients are seen quarterly for routine visits as well as for hospital follow-up and sick visits, and the pharmacist is available to meet with patients at these visits. A scoring system would be useful to ensure time in clinic is prioritized to patients who would benefit the most and could allow for assessment of the impact of medication changes over time.

The Medication Regimen Complexity Index (MRCI;

Table 1. Patient-Related Characteristics

	Initial (n = 113)	Final
Sex, n (%), female	61 (54)	—
Age, mean ± SD, yr	12.2 ± 3.9	12.6 ± 3.9
Medications		
Total number, mean ± SD	12 ± 4.5	12 ± 4.9
Number of inhaled, mean ± SD	4 ± 1.6	4 ± 1.6
BMI percentile, mean ± SD, %	50.4 ± 25.4	52.4 ± 25.9
FEV_1, mean ± SD, %	89 ± 17.2	89 ± 16.7
Party responsible for medication management, n (%)		
Patient	9 (8)	—
Parent/caregiver	76 (67)	—
Both patient and parent/caregiver	28 (25)	—

FEV_1, forced expiratory volume in 1 second

Supplemental Figure) is a reliable and validated 65-item tool for quantifying drug regimen complexity based on the quantity of medications, dosage forms, dosing frequencies, and additional or special instructions.[5] Higher weights are assigned for factors such as dosage forms with less convenient administration, recommended administration intervals, and any additional instructions such as "multiple units at once." Scores can range from zero to infinity with higher scores indicating more complex medication regimens. The MRCI has been defined for some chronic diseases in adolescent and adult populations and was found to differentiate patient-level complexity, potentially leading to utility as a prospective tool for identification of targeted patients for medication therapy interventions. For example, an adolescent subgroup of patients between 7 and 17 years of age with autism spectrum disorders seen as part of a multidisciplinary transitions of care program had a median MRCI score of 9.5 (range, 0–89).[6] Additionally, MRCI scores ranging between 3 and 46 and 2 and 67.5 have been reported in adult hypertensive and HIV populations, respectively.[7] Although this tool has been studied in other chronic, medically complex populations, no studies have examined how complexity of medication regimen affects clinical endpoints in pediatric patients younger than age 7 or patients with CF.

This study sought to use the electronic MRCI coding tool to establish MRCI thresholds to stratify complexity and evaluate whether an association exists between the MRCI and clinical endpoints in a pediatric CF population. We hypothesized that as medication regimen complexity increases, multiple factors might lead to poor clinical outcomes.

Materials and Methods

This was a single-center, retrospective study performed using existing medical record data. Patients seen at the UNC Pediatric Pulmonary Clinic in 2017 with a diagnosis of CF were included if at least 2 clinical pharmacist practitioner notes at least 6 months apart were documented in the electronic medical record. We excluded patients who had a diagnosis of cystic fibrosis transmembrane conductance regulator (CFTR)-related metabolic syndrome, those who were unable to perform pulmonary functions tests during the respective encounter, and patients older than 20 years of age. The primary outcome studied was the correlation of MRCI score with lung function as measured by the forced expiratory volume in 1 second (FEV_1). Secondary outcomes assessed included correlations of MRCI score with BMI percentile, number of infections requiring oral and intravenous antibiotics, and number of hospital admissions. Endpoints were collected from the earliest encounter within the study time frame to the most recent encounter for each patient to assess reproducibility of our results.

We identified patients using a patient list maintained by the clinic pharmacist and CF center. Demographics, outpatient encounter dates, and time between encounters were collected. The party responsible for medication management, assessment of adherence, FEV_1, BMI percentile, and prescribed medications and instructions for use were extracted from the respective encounter. Medication dosage form, frequency of dosing, and additional directions for use were recorded and used to determine the complexity of the medication regimen.

The MRCI was computed using the Microsoft Access Version 1.0 data capture tool developed by the University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, which is publicly available online.[5] Each patient encounter was assigned a unique identifier, and their prescribed medication list at that visit was coded by a clinical pharmacist in accordance with our data collection protocol. Before starting the coding process, the study team created a data col-

Table 2. MRCI Scores and Correlation With FEV_1

Initial MRCI Score	Initial FEV_1, r (p value)	Final MRCI Score	Final FEV_1, r (p value)
Initial MRCI score (N = 113)	−0.323 (0.0005)	Final MRCI score	−0.287 (0.0021)
Low score (n = 16)*	−0.349 (0.18)	Low score (n = 15)*	−0.061 (0.83)
Medium score (n = 88)†	−0.222 (0.04)	Medium score (n = 87)†	−0.094 (0.38)
High score (n = 9)‡	−0.126 (0.75)	High score (n = 11)‡	0.068 (0.84)

FEV_1, forced expiratory volume in 1 second; MRCI, Medication Regimen Complexity Index
* Low MRCI score = 3–33.
† Medium MRCI score 34–66.
‡ High MRCI score 67–101.

lection protocol with detailed coding instructions for common CF medications such as airway clearance therapies, pancreatic enzymes, inhaled antibiotics, and multivitamins to ensure consistency in scoring.

Descriptive statistics were used to analyze patient-related characteristics. Further statistical analysis of primary and secondary endpoints was conducted using Stata statistical software (StataCorp LLC, College Station, TX). The Spearman rank correlation was used to calculate correlations because some of our data were non-parametric. Level of significance was set a priori as ≤ 0.05.

Results

A total of 335 patients were identified for inclusion in this study. Two hundred twenty-two patients were excluded for the following reasons: fewer than 2 outpatient pharmacy visits (n = 168), ≤ 5 or ≥ 20 years of age (n = 36), unable to perform pulmonary function test at ≥ 2 outpatient encounters (n = 12), and patients with CFTR-related metabolic syndrome (n = 6). A total of 113 patients were included in the study. The majority of the study population were female with an average age of 12.2 years at the initial encounter (Table 1). Parents or caregivers of the patient were primarily responsible for medication management. The average number of medications a patient took per day was 12, of which 4 medications were inhaled.

At the time of the initial encounter, the average MRCI score was 46 (range, 3–101). At the time of the final encounter, the average MRCI score was 47 (range, 2–97). We divided the MRCI scores into tertiles, low (3–33 points), medium (34–66 points), and high (67–101 points), to determine if a clinically meaningful threshold existed. Overall, there was a statistically significant association between MRCI score and lung function for both encounters: initial MRCI score and initial FEV_1 (r = −0.323, p = 0.0005) and final MRCI score and final FEV_1 (r = −0.287, p = 0.0021), indicating higher MRCI scores were associated with lower FEV_1 (Table 2).

A negative correlation was found between initial and final MRCI scores and initial and final BMI percentiles (r = −0.162, p = 0.087 and r = −0.125, p = 0.188), indicating lower MRCI scores are associated with higher BMI, but these findings were not statistically significant (Table 3). A significant association between MRCI scores and the number of hospital admissions was found for both initial and final encounters (r = 0.440, p < 0.0005 and r = 0.474, p < 0.0005). Finally, for both encounters, MRCI scores were positively correlated with infections requiring oral antibiotics (r = 0.455, p < 0.0005 and r = 0.236, p = 0.012) and infections requiring intravenous antibiotics (r = 0.338, p = 0.0003 and r = 0.458, p < 0.0005).

Discussion

The MRCI tool was created on the basis that multiple and unique dosage formulations, dosing frequencies, and additional instructions complicate a patient's ability to maintain appropriate and consistent medication administration practices. To date, there are no studies that have investigated the association of the MRCI with clinical outcomes in a CF patient population. The results of our study are broadly generalizable and can be applied to a pediatric CF population between 5 and 20 years of age.

This study demonstrates that a statistically significant association exists between MRCI scores and FEV_1, as well as the number of infections requiring antibiotics and number of hospital admissions. These initial findings suggest that pediatric patients with CF with more complex medication regimens at any outpatient encounter are more likely to have decreased lung function, require more antibiotics, and may be at increased risk for hospital admission. Surprisingly, no statistically significant association exists between MRCI scores and BMI percentile, an important secondary marker of disease severity, in the CF population. This finding is unexpected, and a larger study is needed to determine if a true correlation between medication regimen complexity and nutritional status exists.

Based on the results found, a need exists for a thorough, patient-specific medication review at each outpatient encounter to recognize and suggest possible solutions to medication barriers. As medication experts of the patient care team, pharmacists are positioned as the ideal healthcare professional to take part in these interventions. At UNC Medical Center, a sole clinical pharmacist practitioner was responsible for assisting

Table 3. MRCI Scores and Correlation With BMI Percentile, Hospital Admissions, and Infections Requiring Antibiotics

Variable	BMI Percentile, r	Hospital Admissions, r	Infections Requiring Oral Antibiotics, r	Infections Requiring IV Antibiotics, r
Initial MRCI score	−0.162	0.440*	0.455*	0.338*
Low (n = 16)†	−0.312	0.196	0.673*	0.196
Medium (n = 88)‡	−0.128	0.364*	0.223*	0.304*
High (n = 9)§	0.569	0.461	0.043	0.487
Final MRCI score	−0.125	0.474*	0.236*	0.458*
Low (n = 15)†	−0.223	0.140	0.446*	—
Medium (n = 87)‡	−0.096	0.435*	−0.019	0.336*
High (n = 11)§	0.210	0.5477	0.259	0.057

MRCI, Medication Regimen Complexity Index
* $p < 0.05$.
† Low MRCI score = 3–33.
‡ Medium MRCI score 34–66.
§ High MRCI score 67–101.

with medication management for our entire pediatric CF patient population during the study period. The MRCI tool takes approximately 5 minutes per patient to complete manually, and completion of the tool, in advance of clinic, can assist the pharmacist with prioritization of those patients who would benefit most from a focused, comprehensive medication review during their clinic visit. Given the extensive pharmacotherapy knowledge pharmacists acquire during didactic instruction and post-graduate training, they are able to effectively identify opportunities to simplify a patient's medication regimen.[8] Potential interventions commonly identified by the investigators include prescribing higher pancreatic enzyme strengths to decrease pill burden, discontinuing unnecessary supplemental vitamins if recent levels are within normal limits, and converting to formulations of nebulized antibiotics with fewer administration steps. Further, pharmacists can provide counseling to educate patients and caregivers about new medications, the importance of mainstay therapies, and management of adverse effects and drug interactions. Pharmacists are also knowledgeable about medication-related patient resources available and can help navigate the complexities of receiving medications from multiple pharmacies.[8] These interventions would likely increase adherence to the complex medication regimens patients with CF are commonly prescribed and improve clinical endpoints.

A major strength of this study is the replication of significant associations found in 2 unrelated samples, initial and final encounters. The easily accessible and validated MRCI tool in conjunction with our data collection protocol allow our methodology to be reproduced in another CF center if desired. Finally, the moderate sample size with broad inclusion and minimal exclusion criteria, increase the generalizability of these findings.

There are several limitations to this study. First, it is limited by the intrinsic biases of a retrospective, single-center design. Ideally, in future prospective studies, an adherence tool would be paired with the MRCI tool to determine if poorer clinical outcomes are tied to adherence as opposed to other barriers such as susceptibility patterns, medication intolerances, patient resources, or medication access. Additionally, our study period of 1 year, although representative of a general pediatric CF population between 5 and 20 years of age, was relatively short. Furthermore, CF is a progressive disease, and as patients age, we anticipate their need for additional therapies to treat disease complications will increase. Because ours is the only study assessing medication regimen complexity in patients with CF to date, future studies controlling for age and common disease manifestations are necessary.

Conclusions

Pediatric patients with CF who are on more complex medication regimens have significantly decreased lung function as measured by FEV_1. Medication regimen complexity may also be a predictor for patients who will more frequently require oral and intravenous antibiotics and are more likely to be admitted to the hospital. Pharmacists are trained to identify and address medication-related barriers, and the MRCI tool can be used to prioritize which patients would benefit most from targeted interventions and more frequent follow-up with a pharmacist. Larger studies are needed to determine what impact medication regimen complexity has on growth in the CF population.

Article Information

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Disclosure. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all data and take responsibility for the integrity and accuracy of the data analysis.

Ethical Approval and Informed Consent. The study protocol was approved by the UNC Institutional Review Board (IRB). Written informed consent was not required by the IRB.

Acknowledgments. This work was presented previously at the 28th Annual Pediatric Pharmacy Association Group Meeting on April 10–14, 2019, in Oklahoma City, OK; and at the 33rd Annual North American Cystic Fibrosis Conference on October 31–November 2, 2019, in Nashville, TN.

Submitted. March 3, 2020

Accepted. June 9, 2020

Supplemental Material. DOI: 10.5863/1551-6776-26.3.248.S

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