

# Pulmonary Medication Adherence and Health-care Use in Cystic Fibrosis

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**BACKGROUND:** Poor treatment adherence is common in cystic fibrosis (CF) and may lead to worse health outcomes and greater health-care use. This study evaluated associations of adherence to pulmonary medications, age, health-care use, and cost among patients with CF.

**METHODS:** Patients with CF aged  $\geq 6$  years were identified in a national commercial claims database. A 12-month medication possession ratio (MPR) was computed for each pulmonary medication and then averaged for a composite MPR (CMPR) for each patient. The CMPR was categorized as low ( $< 0.50$ ), moderate (0.50-0.80), or high ( $\geq 0.80$ ). Annual health-care use and costs were measured during the first and second year and compared across adherence categories by multivariable modeling.

**RESULTS:** Mean CMPR for the sample ( $N = 3,287$ ) was  $48\% \pm 31\%$ . Age was inversely related to CMPR. In the concurrent year, more CF-related hospitalizations were observed among patients with low (event rate ratio [ERR], 1.35; 95% CI, 1.15-1.57) and moderate (ERR, 1.25; 95% CI, 1.05-1.48) vs high adherence; similar associations were observed for all-cause hospitalizations and CF-related and all-cause acute care use (hospitalizations + ED) in the concurrent and subsequent year. Rates of CF-related and all-cause outpatient visits did not differ by adherence. Low and moderate adherence predicted higher concurrent health-care costs by \$14,211 (\$5,557-\$24,371) and \$8,493 ( $-\$1,691$  to \$19,709), respectively, compared with high adherence.

**CONCLUSIONS:** Worse adherence to pulmonary medications was associated with higher acute health-care use in a national, privately insured cohort of patients with CF. Addressing adherence may reduce avoidable health-care use.

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**ABBREVIATIONS:** CF = cystic fibrosis; CMPR = composite medication possession ratio; ICD-9-CM = *International Classification of Diseases, Ninth Revision, Clinical Modification*; MPR = medication possession ratio

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Recent advances in the treatment and aggressive management of cystic fibrosis (CF) have led to significant improvements in prognosis, with median predicted survival reaching 37 years.<sup>1</sup> However, daily management requires a complex, time-consuming treatment regimen to address the multisystem effects of CF.<sup>2</sup> Long-term use of one or more pulmonary medications is recommended,<sup>3</sup> which can include inhaled antibiotics (eg, tobramycin, colistin, aztreonam) and oral azithromycin and nebulized mucolytic agents (eg, dornase alfa, hypertonic saline).<sup>3,4</sup> The burden of treatment and poor adherence have emerged as critical issues in the daily management of CF.<sup>5,6</sup>

Prior analyses of objective adherence data have reported low rates of adherence to individual pulmonary medications among patients with CF, ranging from 31% to 79%.<sup>7-12</sup> Most of these studies were limited by small sample sizes and limited age ranges. Furthermore, little is known about how rates of adherence to pulmonary medications vary across the life span from childhood through older adulthood, although there appears to be a significant decrease in adherence during adolescence.<sup>13,14</sup> Adherence may also affect health-care use and costs. Two studies

found that worse adherence to inhaled tobramycin was associated with increased risk of hospitalization and health-care costs,<sup>15,16</sup> whereas one-third found no association between dornase alfa adherence and inpatient respiratory exacerbations but a trend toward higher overall health-care charges.<sup>17</sup> Lower overall pulmonary medication adherence (average adherence to dornase alfa, hypertonic saline, azithromycin, and inhaled tobramycin) was also associated with greater occurrence of pulmonary exacerbations requiring IV antibiotics and lung function testing in a retrospective medical record review of patients with CF.<sup>5</sup> To our knowledge, no study has assessed the associations between overall adherence to long-term pulmonary medications and age, health-care use, and health-care costs in CF.

Using retrospective claims data for privately insured patients with CF, this study measured drug-specific and overall adherence to pulmonary medications and assessed variations in overall adherence across demographic subgroups and their associations with health-care use. We hypothesized that poorer overall medication adherence would be associated with older age and higher health-care use and costs.

## Materials and Methods

### *Data Source and Sample Selection*

The Thomson Reuters MarketScan Commercial Claims and Encounters Database (January 2005 to June 2011) includes medical and drug data for active employees and their dependents with primary coverage through employer-sponsored private health insurance throughout the United States.<sup>18</sup> The MarketScan claims database offers the largest claims capture of physician office visits; hospital stays; retail, mail-order, and specialty pharmacies; and carve-out care. The database undergoes extensive validity and editing procedures to ensure high quality and consistency and has been presented in > 400 peer-reviewed articles.

Patients included in this retrospective cohort study met the following criteria: (1) two or more independent CF diagnoses (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM], code 277.0X) during medical visits occurring  $\geq 30$  days apart, (2) one or more prescription fills for a pulmonary medication (azithromycin, dornase alfa, hypertonic saline, or an inhaled antibiotic [aztreonam, colistin, or tobramycin]), and (3) continuous enrollment for  $\geq 180$  days. For each patient meeting these criteria, the end date of the first 180-day continuous enrollment period and the end dates of subsequent 365-day periods were defined as potential index dates. An index date was randomly chosen among all potential index dates meeting the following additional inclusion criteria: (4) continuous enrollment for  $\geq 365$  days after the index date, (5) a filled prescription for a pulmonary medication within the prior 90 days, and (6) age  $\geq 6$  years.

### *Measures*

For each long-term pulmonary medication filled  $\leq 90$  days before the index date, adherence was calculated as the medication possession ratio (MPR), that is, the cumulative days' supply of medication dispensed divided by 365 days after the index date (excluding hospitalized days). Values were truncated to 100%. Drug-specific MPRs were calculated for each pulmonary medication and then averaged to obtain a composite MPR (CMPR).

CMPR was converted to a categorical variable as follows: low ( $< 0.50$ ), moderate ( $0.5 \leq \text{CMPR} < 0.80$ ), and high ( $\geq 0.80$ ).<sup>5</sup> Additional details for this calculation appear in e-Appendix 1 and e-Tables 1 and 2.

Health-care use and costs were measured for two time periods to assess the prospective relationship with adherence: (1) the first year (365 days) after the index date to assess concurrent associations with adherence and (2) the second year after the index date (ie, 365 days after index date + 365 days). Use included hospitalizations and ED, outpatient, and acute care (hospitalizations + ED) visits. Costs included the sum of hospitalizations, ED, and outpatient charges adjusted for inflation to 2011 US dollars. All-cause and CF-related health-care use and costs were evaluated; medical visits were considered CF related if associated with a CF diagnosis (ICD-9-CM code 277.0X). Pharmacy costs were not included. Baseline characteristics included demographics, index year, comorbidities, number of medications, and medication copayment. Comorbidities were identified on the basis of at least one claim associated with the corresponding ICD-9-CM code and required to be present during the 180-day baseline period.

### *Statistical Analysis*

Mean CMPRs were compared across patient subgroups, including age, sex, and number of pulmonary medications dispensed  $\leq 90$  days preceding the index date. Between-group differences were assessed with Wilcoxon rank sum tests. Health-care use was compared across CMPR levels using unadjusted and adjusted event rate ratios estimated from univariable and multivariable negative binomial regression models, respectively. Unadjusted differences in costs were tested with Wilcoxon rank sums. Multivariable generalized linear models with a  $\gamma$ -distribution and a log link were used to estimate adjusted cost differences, with statistical significance assessed through nonparametric bootstrap resampling with 499 iterations. All multivariable models were adjusted for age, sex, comorbidities, index year, number of medications, and medication copayment at baseline. All analyses were conducted with SAS 9.2 (SAS Institute Inc) statistical software.

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