The Geographic Impact on Hospitalization in Patients with Cystic Fibrosis

Benjamin T. Kopp, MD[1,2], Lisa Nicholson, PhD[3], Grace Paul, MD[1], Joseph Tobias, MD[4], Chandar Ramanathan, MD[1], and Don Hayes, Jr, MD, MS[1]

Objective To assess whether geographic location influences hospitalizations for pulmonary exacerbations for patients with cystic fibrosis (CF) in the US, as there is no existing literature regarding this subject.

Study design The CF Foundation Patient Registry was analyzed during the years 2007-2012 via geographic grouping of states. The impact of geographic region on recovery from hospitalization, hospitalization length, and time to next hospitalization were analyzed using multivariate models.

Results Posthospitalization lung function and nutritional measures were similar among regions for 1 year following hospitalization. The West region was associated with risk of longer hospital stays (OR 1.60, CI 1.45-1.77), however, dornase alfa use (OR 3.85, CI 1.15-12.92) was the only specific factor. History of allergic bronchopulmonary aspergillosis (OR 1.58, CI 1.11-2.25) and adult age (OR 2.48, CI 1.17-5.25) in the Northeast, chronic macrolide use in the South (OR 1.36, CI 1.03-1.79), and infection with *Candida albicans* (OR 1.47, CI 1.18-1.82) and *Pseudomonas aeruginosa* (OR 1.44, CI 1.02-2.04) in the Midwest were associated with increased hospitalization length. There was a significantly decreased risk for subsequent hospitalizations in the Northeast compared with other regions ($P = .038$). Sociodemographic analysis identified Caucasians in the South having a significantly lower risk of future hospitalization compared with African Americans (hazard ratio 0.79, CI 0.69-0.91, $P = .0009$).

Conclusions There is significant regional variability in hospitalization length and risks for subsequent hospitalizations for patients with CF in the US. Regional variation should be subject to further study to determine if benchmarking standards can be achieved nationally. *(J Pediatr 2016;170:246-52)*.

Despite significant therapeutic advances over the last decade, cystic fibrosis (CF) continues to be associated with prominent morbidity and mortality attributable primarily to pulmonary exacerbations. These periodic pulmonary exacerbations result in lengthy hospitalizations for aggressive intravenous (IV) antimicrobial therapy, airway clearance, and nutritional support. Hospital stays for CF are associated with worsening structural lung changes including bronchiectasis, and poorer longitudinal nutritional outcomes.[1] In addition, hospitalizations are linked with poorer quality of life and significant treatment burden for the population with CF.[2] Recovery from a CF pulmonary exacerbation, or lack thereof, is a significant predictor of long-term lung function decline.[3] Patients with less than 6 months between exacerbations experience the greatest decline in lung function, emphasizing the importance of accurately predicting those patients at highest risk of pulmonary exacerbation.[3]

With the expanded use of patient registries and longitudinal cohort studies, much information has been determined regarding risk factors for pulmonary exacerbation and the need for therapeutic interventions in CF. Although extended hospital stays for IV antibiotics are common for treatment of a CF exacerbation, the location of this treatment (home vs hospital) does not affect long-term pulmonary outcomes in CF, or the time to next exacerbation.[4] However, specific environmental factors may play a role in pulmonary exacerbation risk in CF, because air pollution is associated with increased antibiotic use, increased risk of pulmonary exacerbation, and a decline in lung function.[5,6] In addition, hospitalization for pulmonary exacerbation in CF is associated with a failure to return to baseline lung function in nearly 25% of children.[7] It is unknown whether geographic location affects pulmonary exacerbation in CF. As a corollary to exacerbation risks, hospital length of stay (LOS) varies across the US for adults with CF,[8] but pediatric data are unknown. It is also unknown if there are specific regional variates that are risk factors for increased LOS regionally.

Recently, we identified significant regional variations in the distribution of respiratory pathogens, chronic medication usage, comorbidities, and patient demographics for patients with CF in the US.[9] Although these factors did not

BMI	Body mass index
CF	Cystic fibrosis
CFFPR	CF Foundation Patient Registry
FEV_1	Forced expiratory volume in one second
HR	Hazard ratio
IV	Intravenous
LOS	Length of stay
NIS	Nationwide Inpatient Sample

From the [1]Section of Pulmonary Medicine, Nationwide Children's Hospital; [2]Center for Microbial Pathogenesis, The Research Institute at Nationwide Children's Hospital; [3]Institute for Population Research, The Ohio State University; and [4]Department of Anesthesiology and Pain Medicine, Nationwide Children's Hospital, Columbus, OH

B.K. and J.T. are funded by Nationwide Children's Hospital. B.K. and D.H. are funded by the CF Foundation. The authors declare no conflicts of interest.

Portions of this work were presented at the North American Cystic Fibrosis Conference, Atlanta, GA, October 9–11, 2014.

http://dx.doi.org/10.1016/j.jpeds.2015.11.012

influence overall regional mortality rates, the incidence of CF mortality remained low in the US from year to year. Therefore, in the current study, we sought to analyze the US CF Foundation Patient Registry (CFFPR) to determine whether previously discovered regional variates may have a role in affecting more common outcomes such as hospital LOS and the subsequent recovery from hospitalization. We hypothesized that regional variates impact hospital LOS and time to next hospitalization.

Methods

This study was deemed exempt from institutional review (IRB11-00415). We obtained permission from the CFFPR to analyze registry data for this study. Data were analyzed from the CFFPR during a 5-year period from 2007-2012. The CFFPR is comprised of nearly 31 000 individuals who receive care in CF Foundation-accredited care centers in the US.[10] For the purpose of geographic classification, patients were classified according to their state of residence and then further classified into geographic regions according to the Nationwide Inpatient Sample (NIS; **Figure** available at www.jpeds.com).[11]

Study variables were first identified at the individual level, and the individual's region was determined by the state information provided according to the classification above. CF was defined as 2 disease-causing mutations or a sweat chloride test ≥60 mmol/L. All registry participants with information on state of residence were eligible for analysis (n = 30 896). New births and deaths during the study period were included, but subjects had to have at least 1 year of data prior to death for study inclusion. During the hospitalization analysis, a threshold of 10 days was used to identify prolonged stays as our previous analysis demonstrated that both pediatric and adult hospitalizations averaged less than 10 days per hospitalization across the US.[8] Hospitalizations of 14 days or more were examined in a subanalysis. A pulmonary exacerbation and its subsequent length were determined by using the CFFPR registry variable "number of days with pulmonary exacerbation." For the time to next hospitalization analysis, subjects were included if they had a second hospitalization for pulmonary exacerbation during the study period within 365 days of their first recorded hospitalization, as long as the hospitalization lasted more than one night. Only the first two hospitalizations were included per subject for analysis in order to power the models. Further detail on data variables is included in the **Appendix** (available at www.jpeds.com).

Statistical Analyses

Because of extensive missing data on forced expiratory volume in one second (FEV_1), especially among children < 10 years of age with more than 50% of cases missing, subset-analysis of changes in FEV_1 and body mass index (BMI) at 3, 6, 9, and 12 months posthospitalization for pulmonary exacerbation was conducted. We examined changes in FEV_1 and BMI at this time intervals across all 4 regions using ANOVA analyses with Tukey corrections for multiple comparisons.

Propensity score matching was used to generate propensity scores for each case in our sample. The propensity score was defined as the probability of living in a given region conditioned based on a patient's observed characteristics. The effect of living in a given region on extended hospitalization for patients with similar values on the propensity score was then estimated using the psmatch2 function available in Stata v 13 (StataCorp, College Station, Texas). Specifically, we used the approach of pairs of treated and untreated subjects (in our case individuals living in a given region vs all other regions) formed such that the difference in propensity scores between matched subjects differed by at most a fixed distance (caliper width). In addition, samples were matched without replacement, such that each subject could be included in at most one matched set.

In order to examine potential residual variation in baseline distributions of characteristics, multivariable logistic regression analyses clustered on state of residence were also examined to test the relationship between region of residence and extended hospitalization. To be consistent with the propensity score matching models, four separate models were also run examining one region at a time compared with all other regions. In order to compare the effects of each characteristic across regions multivariable logistic regression results, as noted above, were stratified by region.

Kaplan-Meier survival curves were computed for all demographic and clinical variables described above for each subgroup of individuals living in each of the 4 regions examined (West, Midwest, Northeast, and South). The time to next hospitalization or censoring was expressed as time in days. We derived unadjusted hazard ratios (HRs) (univariate) for time to next hospitalization in each subgroup by using a Cox proportional hazards regression. Log-log plots were done to verify that the proportional hazard assumption was not violated.

We then used a multivariable Cox regression model to examine clinical and demographic factors that might be associated with time to next hospitalization within each given region to look for potential differences in predictors across regions. All factors deemed clinically important were included in the models regardless of statistical significance determined from Kaplan-Meier plots. Stata Statistical Software v 13.0 (StataCorp) was used for all analyses. All statistical tests were 2-sided, with statistical significance set at the 0.05 level.

Results

The demographic breakdown of the overall cohort was described previously[9] and is listed in the **Table I** (available at www.jpeds.com).

Hospitalization Impact on FEV_1 and BMI Recovery

Regional differences in FEV_1 and BMI for 1 year following hospitalization for a pulmonary exacerbation were calculated and are outlined in **Table II**. There were statistically, but not clinically, significant inter-regional differences in FEV_1 at 6 and 12 months posthospitalization. Reduction in FEV_1 for