Predictors and Outcome of Low Initial Forced Expiratory Volume in 1 Second Measurement in Children with Cystic Fibrosis

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Objective To identify the characteristics of children with cystic fibrosis with low initial forced expiratory volume in 1 second (FEV_1) % predicted and to investigate their outcome.

Study design Patients were categorized into low or high initial FEV_1 groups using cluster analysis. Comparisons of the demographic and clinical data were performed between the 2 groups.

Results From 122 children, 21 clustered into the low and 101 into the high FEV_1 group. The mean FEV_1 was 69% ± 12% predicted for the low and 95% ± 12% predicted for the high FEV_1 group ($P < .001$). The low FEV_1 group had lower body mass index percentiles ($P = .003$), were hospitalized more frequently ($P = .001$), and had been on dornase alfa longer ($P = .006$). Low FEV_1 group had more patients with positive cultures for *Pseudomonas aeruginosa* ($P = .002$) and *Stenotrophomonas maltophilia* ($P < .001$) and had more total number of cultures positive for mucoid *P aeruginosa* ($P = .009$) and methicillin resistant *Staphylococcus aureus* + *P aeruginosa* ($P = .005$). The low FEV_1 group continued to have low FEV_1 measurements, their FEV_1 declined slower, required more hospitalizations per year ($P = .01$), and had more cultures for mucoid ($P = .003$) and nonmucoid *P aeruginosa* ($P = .02$) ± methicillin resistant *S aureus* ($P = .002$) in comparison with the high FEV_1 group. Poor adherence was associated with lower initial FEV_1 values in females, and early, rapid decline of FEV_1 in males.

Conclusions Some children with cystic fibrosis may present with poor lung function early in life and continue to have subnormal lung function associated with reduced body mass index, more frequent hospitalization, and higher rates of infection. Such children may benefit from careful evaluation and close follow-up. *(J Pediatr 2014;164:832-8)*.

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Progressive lung disease is the major cause of morbidity and mortality in individuals with cystic fibrosis (CF). Therefore, identification of pulmonary disease at an early stage may be helpful to prevent loss of lung function in children with CF. The forced expiratory volume in 1 second (FEV_1) is currently the standard measure to assess pulmonary morbidity in individuals with CF.[1-3] However, acceptable spirometry results are difficult to achieve in many preschoolers.[2,4] Therefore, early lung disease in young children may remain unrecognized if symptoms and chest imaging findings are subtle, and may be treated suboptimally until the first successful spirometry maneuver. Understanding the conditions that may lead to loss of lung function early in life, years before the initial successful spirometry, may help clinicians to identify these vulnerable children.

Early and recent reports indicate the importance of nutritional health in pulmonary outcomes.[3-8] A study of nutrition and growth in children with CF found that pulmonary function at age 6 years could be predicted by weight-for-age, height-for-age, and percent ideal body weight at age 3 years.[3] Greater weight at age 4 years was associated with greater height, better pulmonary function, and better survival.[8] Other studies showed that early acquisition of *Pseudomonas aeruginosa*[9] and conversion of nonmucoid *P aeruginosa* to mucoid or multidrug-resistant phenotypes[10] have been associated with more rapid progression of lung disease in CF. However, there are still many unknowns regarding the genetic and environmental modifiers, clinical characteristics, and predictors associated with early lung disease in children with CF.

In this study, our first aim was to identify children with CF and low FEV_1 % predicted measurements during their initial spirometry and, using a cluster analysis, to determine the patient characteristics associated with low initial FEV_1 % predicted

BAL	Bronchoalveolar lavage
BMI	Body mass index
CF	Cystic fibrosis
CFRD	CF-related diabetes
CFTR	Cystic fibrosis transmembrane regulator
FEV_1	Forced expiratory volume in 1 second
MRSA	Methicillin resistant *Staphylococcus aureus*
NTM	Nontuberculous mycobacterium

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measurements. The second aim was to compare the outcomes of children with low initial FEV_1 with children with high FEV_1 % predicted and to determine whether initial low FEV_1 measurements persist over years.

Methods

A retrospective review of medical records of children with CF followed at Arkansas Children's Hospital Cystic Fibrosis Care Center was performed. This study was approved by the Institutional Review Board at University of Arkansas for Medical Sciences. Children who were diagnosed with CF before age 3 years followed at the center for a minimum of 2 consecutive years prior to and after their initial acceptable spirometry were identified (1985-2009). Demographic data included sex, race, age at diagnosis of CF, CF transmembrane regulator (CFTR) mutation, sweat chloride levels, age of initial acceptable spirometry, type of medical insurance, and the distance between the patient's home and the CF care center. Number of patients receiving mucolytic agents (dornase alfa) and inhaled antibiotic (tobramycin) and the duration of use of these medications were recorded.

Variables associated with nutritional status included pancreatic insufficiency status, weight-for-age, height-for-age, and body mass index (BMI) percentiles. All nutrition-related measurements were included from the time of initial diagnosis of CF until the end of the study. Existence of CF-related liver disease and CF-related diabetes (CFRD) were recorded. Respiratory cultures obtained during each clinical encounter and frequency of hospitalizations were recorded before and after the initial spirometry. Positive respiratory culture is defined as at least 1 positive culture during the study period and patients with $\geq$1 positive culture for CF-related pathogens were included in the infection cohort.

Adherence was assessed objectively by medication refill history when available. Adherence was classified as poor if the medication refill rate was <50%, fair when it was between 50% and 80%, and good when it was >80%. American Thoracic Society criteria[11] were used to define a valid initial spirometry. The reference equations of Wang et al[12] were used to calculate FEV_1 % predicted values. Yearly decline in FEV_1 % predicted and estimated slopes were calculated. Outcome measures included death, history of lung transplant (or listed for lung transplant), and frequency of hospitalization. Identified potential risk factors for poor pulmonary health included positive respiratory cultures for methicillin resistant *Staphylococcus aureus* (MRSA), nonmucoid and mucoid *P aeruginosa*, nontuberculous mycobacterium (NTM), *Burkholderia cepacia* complex and *Stenotrophomonas maltophilia,* and diagnosis of CFRD.

Statistical Analyses

All data were analyzed using R v. 2.14.1 (R Development Core Team, Vienna, Austria). All acceptable FEV_1 % predicted measurements were used for the statistical analysis. The best and the worst yearly FEV_1 % predicted were defined as the highest and the lowest measurements within a calendar year. Cluster analysis was performed to categorize patients with similar initial FEV_1 % predicted measurements by using the best and the worst FEV_1 % predicted measurement of the calendar year following the initial spirometry. Based on the Wald minimum-variance hierarchical clustering method, patients were merged into larger groups to minimize the change in error sum of square (loss of information) at each generation of clusters. Two final groups with low and high initial FEV_1 % predicted were identified. We compared the demographic and clinical data prior with the initial FEV_1 % predicted measurements between the low and high FEV_1 groups using the 2-sample *t* test for the continuous variables and the χ^2 test for the categorical variables. Outcome measures (eg, yearly decline in FEV_1 % predicted, history of lung transplant, mortality, CFRD, and frequency of hospitalization) were compared between low and high initial FEV_1 groups. Similar comparisons also were performed for the frequency of respiratory tract pathogens.

Repeated measures analyses were used to estimate mean rates of change in FEV_1 % predicted by using all yearly FEV_1 % predicted measurements, and estimated FEV_1 % predicted slopes were compared between high and low FEV_1 groups. Longitudinal analyses were further carried out to evaluate the effects of group, adherence, and sex on the repeated measured FEV_1 % predicted over time using the generalized least squares. A compound symmetry covariance structure was used to account for the correlation between different FEV_1 measurements from the same patient. Restricted cubic spline was used to account for the nonlinear effect of exam age using 3 knots. *P* values of <.05 were considered to indicate statistical significance.

Results

One hundred twenty-two children met the inclusion criteria. All children were diagnosed based on symptoms of CF, except those who were siblings of a child with CF, as newborn screening was not initiated in Arkansas until 2008. The median age at diagnosis of CF was 4 months (IQR 2-12). The mean age at initial acceptable spirometry was 6 years (SD 1 year). Sixty-six (54%) participants were male. Seventy-four (61%) were homozygous for F508del-CFTR, 37 (30%) were heterozygous for F508del-CFTR, and 9 (7%) had mutations other than F508del-CFTR. The initial cluster analyses revealed 4 groups of children with similar initial, best, and worst FEV_1 % predicted measurements during the first year of acceptable spirometry. Initial FEV_1 % predicted values were clearly lower in one group compared with the other 3 groups (**Figure 1**). Therefore, 3 groups with higher initial FEV_1 % predicted were combined and defined as the high FEV_1 group. The remaining group was defined as the low FEV_1 group.

Table I shows the mean values of the initial FEV_1 % predicted and the best and the worst measurements of the first year for the low FEV_1 and high FEV_1 groups. There