Improvements in Lung Function Outcomes in Children with Cystic Fibrosis are Associated with Better Nutrition, Fewer Chronic *Pseudomonas aeruginosa* Infections, and Dornase Alfa Use

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Objective To compare lung function and nutritional outcomes in cystic fibrosis (CF) for 2 birth cohorts in our CF center.

Study design Patients with CF born between 1985 and 2000 treated in our CF center before age 5 years were included. The patients were divided into 2 equal birth cohorts for comparison: birth cohort 1 (born between 1985 and 1992) and birth cohort 2 (born between 1993 and 2000). To compare lung function, we used forced expiratory volume in the first second (FEV_1)% predicted and FEV_1% predicted slope from age 6 to 12 years. We hypothesized that we would find significant improvements in lung function and nutritional outcomes in our patients with CF.

Results The patients born between 1993 and 2000 (birth cohort 2) had better lung function, a slower rate of decline in lung function, and better nutritional outcomes compared with those born between 1985 and 1992 (birth cohort 1). Factors associated with a slower rate of decline in lung function in both groups were a higher baseline body mass index (BMI)%, a slower BMI% rate of decline, absence of chronic *Pseudomonas aeruginosa* respiratory infection, and initiation of dornase alfa (Pulmozyme) therapy before age 9 years.

Conclusion Our results demonstrate dramatically improved lung function and nutritional outcomes in the children with CF in our center. The improvements in lung function outcomes are associated with better nutrition, fewer chronic *P aeruginosa* infections, and dornase alfa therapy. *(J Pediatr 2008;153:752-7)*

In patients with cystic fibrosis (CF), chronic pulmonary infection and inflammation result in progressive loss of lung function and early death due to respiratory failure. Lung function in patients with CF is assessed at each clinical encounter and is an important predictor of mortality and survival.[1-4] There have been major advances in CF care in recent decades, with improved nutrition, inhaled antibiotics, inhaled mucolytics, and oral anti-inflammatory therapies. The CF Foundation has published data that demonstrate improvements in lung function and nutritional outcomes in CF from 1990 to 2006.[5] To date, however, no longitudinal study has demonstrated a significant improvement in the rate of decline in lung function in patients with CF. Corey et al[3] analyzed birth cohort data in 366 patients age 5 to 32 years born between 1960 and 1974 and found no differences in the rate of decline in lung function in successive birth cohorts. Que et al[6] analyzed birth cohort data in 318 patients age 18 to 22 born between 1960 and 1984 and reported a nonsignificant trend toward an improved rate of decline in lung function. Our study was designed with an advantage to show improvement: We analyzed FEV_1% predicted solely in young children. The rate of decline in lung function in CF has a direct association with baseline lung function.[7,8] We chose pediatric patients for our statistical analysis because of their higher absolute lung function values and potentially faster rates of decline in lung function.

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METHODS

We reviewed our database for lung function and nutritional data for all patients with CF born between 1985 and 2000 treated in our CF center at the Cincinnati Children's

BMI	Body mass index	Height-for-age%	Height-for-age percentile
BMI%	BMI percentile		
CF	Cystic fibrosis	Weight-for-age%	Weight-for-age percentile
FEV_1	Forced expiratory volume in the first second		

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Hospital Medical Center before age 5 years. The patients were divided into 2 equal birth cohorts: birth cohort 1 (born between 1985 and 1992) and birth cohort 2 (born between 1993 and 2000).

Lung Function Outcomes

Patients with CF with acceptable and repeatable spirometry measures were included in our lung function outcomes comparison. A patient was included in the data set once he or she had performed 3 acceptable and repeatable spirometry sessions, according to American Thoracic Society criteria up to early 2006 and then joint American Thoracic Society–European Respiratory Society criteria thereafter.[9,10] Peak forced expiratory volume in the first second (FEV_1)% predicted at each age for each patient was calculated using absolute FEV_1 values for age 6 to 12 years. The reference equations of Wang et al[11] were used to calculate FEV_1% predicted values. Lung function outcomes were analyzed only for the years 1994 to 2006, because 1994 was the first year for which our database included all spirometry measurements for our patients with CF. Lung function outcomes were compared by birth cohort. The mean peak FEV_1% predicted and the rate of change (slope analysis) in peak FEV_1% predicted at each age from age to 6 to 12 years were analyzed by calculating a slope for each patient with 4 or more yearly data points.

Nutritional Outcomes

Patients with CF with BMI% (percentile), weight for age% (percentile), and height for age% (percentile) documented in our database were included in the nutritional outcomes assessment. Peak BMI%, peak weight for age%, and peak height for age% at each age from 2 to 12 years was obtained. Reference ranges to calculate percentiles were based on data from the National Center for Health Statistics.[12]

Statistical Analysis

Descriptive statistics. Fisher's exact test for association was used to analyze differences in demographic variables, chronic respiratory infection status for *Staphylococcus aureus* and *Pseudomonas aeruginosa*, and dornase alfa (Pulmozyme) use. Chronic infection was defined as 3 consecutive positive respiratory cultures (oropharyngeal, sputum, and/or bronchoalveolar lavage) collected at least 1 month apart before age 13 years. Wilcoxon's rank-sum test was used to assess differences in age at diagnosis and differences in the frequency of clinical visits per year from age 6 to 12 years.

Repeated-measures analysis. Repeated-measures analyses were used to assess the mean peak BMI%, mean peak weight for age%, and mean peak height for age% at age 3, 6, and 12 years; mean peak FEV_1% predicted from age 6 to 12 years; mean rate of change (slope analysis) in peak FEV_1% predicted from age 6 to 12 years; and mean rate of change (slope analysis) in peak BMI%, peak weight for age%, and peak height for age% from age 2 to 10 years, adjusted for covariates of age and sex. Repeated-measures analysis was used to analyze peak FEV_1% predicted at each age from 6 to 12 years as the dependent variable with covariates of age at diagnosis, sex, age, genotype (homozygous Delta F508: yes/no), chronic *S aureus* infection before age 13 years (yes/no), chronic *P aeruginosa* infection before age 13 years (yes/no), long-term dornase alfa use before the FEV_1% predicted measurement was obtained (> 1 year of use: yes/no), baseline FEV_1%, baseline BMI%, and longitudinal peak BMI%.

Regression. A linear regression model was designed to analyze FEV_1% slope (1 slope per subject, calculated from age 6 to 12 years) as the dependent variable with covariates of age at diagnosis, sex, genotype, chronic *S aureus* infection before age 13 years, chronic *P aeruginosa* infection before age 13 years, initiation of dornase alfa therapy before age 9 years, age at the start of slope calculation, baseline FEV_1%, baseline BMI%, and peak BMI% slope.

All statistical analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, North Carolina) software, primarily Proc Freq, Proc Npar1way, and Proc Mixed. A significance level of $\alpha < .05$ was used for all tests reported in this paper. Results are reported as significant mean differences ± standard error of the mean unless noted otherwise.

RESULTS

Lung Function Outcomes

A total of 144 patients with CF born between 1985 and 2000 met the inclusion criteria for comparison of lung function outcomes. There were no significant differences in terms of race, sex, genotype, age of diagnosis, prevalence of pancreatic enzyme supplementation, or prevalence of chronic *S aureus* infection between birth cohort 1 and birth cohort 2 (Table I). Significant differences were found between the 2 cohorts in the prevalence of chronic *P aeruginosa* infection ($P = .002$), the prevalence of long-term dornase alfa use ($P < .001$), and the mean number of clinical visits per year from age 6 to 12 years ($P = .0009$), however (Table I). Birth cohort 2 had a higher mean peak FEV_1% predicted at age 6 ($P = .001$), a higher mean peak FEV_1% predicted from age 6 to 12 ($P < .0001$), and a slower rate of decline in peak FEV_1% predicted from age 6 to 12 ($P = .01$) when adjusted for age and sex (Table II).

Nutritional Outcomes

A total of 155 patients with CF born between 1985 and 2000 met the inclusion criteria for comparison of nutritional outcomes. Birth cohort 2 had a higher mean peak BMI% (percentile), mean peak weight for age% (percentile), and mean peak height for age% (percentile) at age 3, 6, and 12 years compared with birth cohort 1. Birth cohort 2 also had a slower rate of decline in peak BMI% and peak weight for age% from age 2 to 10 (Table II). The rate of decline in peak height for age% did not differ between the 2 groups.

Table I. Descriptive comparison of birth cohorts 1 and 2 for demographic variables, chronic infection status before age 13, and clinical visit frequency from age 6 to 12 years

Variable	Birth cohort 1 (n = 74)	Birth cohort 2 (n = 70)	*P* value
Race, % Caucasian	97.0	98.6	.61
Sex, % female	41.9	48.6	.50
Genetics, % homozygous Delta F508	50.0	62.3	.17
Age of diagnosis, years			
Mean ± standard deviation	0.9 ± 1.3	0.9 ± 1.1	.74
Median	0.23	0.44	
Interquartile range	0.15-0.84	0.07-1.25	
Pancreatic enzyme supplementation, %	98.4	98.6	1.0
Chronic *S aureus* infection, %	54.6	68.1	.11
Chronic *P aeruginosa* infection, %	65.2	37.7	.002
Chronic dornase alfa use before age 12, %	39.4	69.6	<.0001
Clinical visits per year from age 6 to 12			
Mean ± standard deviation	3.6 ± 0.8	4.7 ± 2.0	.0009
Median	3.7	4.0	
Interquartile range	3.3-3.9	3.4-5.1	

Table II. Outcomes comparison of birth cohorts 1 and 2

Outcome measure	Birth cohort 1 (lung function, n = 74; nutritional, n = 73)	Birth cohort 2 (lung function, n = 70; nutritional, n = 82)	*P* value
Peak FEV_1% predicted at age 6	85.6 ± 3.0	97.4 ± 3.5	.001
Peak FEV_1% predicted at age 6 to 12	85.0 ± 2.1	101.36 ± 2.2	<.0001
Rate of decline: peak FEV_1% predicted, percent/year from age 6 to 12	0.58 ± 0.4	−0.91 ± 0.4	.01
Peak BMI%* at age 3	48.3 ± 4.2	60.4 ± 3.1	.02
Peak BMI%* at age 6	45.7 ± 3.7	59.6± 3.1	.004
Peak BMI%* at age 12	41.5 ± 3.8	57.1 ± 5.5	.02
Rate of decline peak BMI%*, %/year from age 2 to 10	1.19 ± 0.29	−0.03 ± 0.36	.009
Peak weight for age%* at age 3	40.6 ± 3.7	52.2 ± 3.0	.02
Peak weight for age%* at age 6	33.9 ± 3.1	48.9 ± 3.0	.0006
Peak weight for age%* at age 12	30.5 ± 3.1	46.4 ± 4.7	.005
Rate of decline peak weight for age%*, %/year from age 2 to 10	1.33 ± 0.28	0.27 ± 0.28	.007
Peak height for age%* at age 3	29.9 ± 3.5	45.1 ± 2.9	.001
Peak height for age%* at age 6	29.5 ± 3.1	41.1 ± 2.9	.008
Peak height for age%* at age 12	28.2 ± 3.2	38.7 ± 3.8	.04
Rate of decline peak height for age%*, %/year from age 2 to 10	−0.12 ± 0.21	0.18 ± 0.18	.28

Shown is a statistical comparison (least squares means estimates ± standard error of the mean) of birth cohorts 1 and 2 for lung function outcomes, calculated using the Wang[11] reference equations, and nutritional outcomes, with percentiles calculated using National Center for Health Statistics[12] reference ranges.
*Percentile.

Predicting FEV_1%. Covariates with significant associations with the mean peak FEV_1% predicted from age 6 to 12 years were baseline FEV_1% ($P < .0001$), longitudinal peak BMI% ($P < .0001$), chronic *P aeruginosa* respiratory tract infection ($P = .012$), and initiation of dornase alfa therapy at least 1 year before lung function measurement ($P = .048$) (Table III). Baseline BMI% ($P = .07$), age at diagnosis ($P = .50$), sex ($P = .95$), and genotype ($P = .58$) were not associated with the peak FEV_1% predicted.

Predicting FEV_1% rate of change. Covariates with significant associations with the FEV_1% slope (rate of change) from age 6 to 12 years were baseline FEV_1% ($P < .0001$), baseline BMI% ($P = .017$), BMI% slope ($P = .0003$), chronic *P aeruginosa* respiratory tract infection ($P = .004$), and initiation of dornase alfa therapy before age 9 years ($P = .028$) (Table IV). Covariates of age at diagnosis ($P = .38$), age when FEV_1% predicted slope was first calculated ($P = .80$), sex ($P = .33$), genotype ($P = .63$), and chronic *S aureus* respiratory tract infection ($P = .96$) were not associated with the FEV_1% rate of change.

DISCUSSION

This longitudinal cohort analysis has demonstrated a statistically significant improvement in the rate of decline in lung function in patients with CF. Studies analyzing the rate

Table III. Factors associated with peak FEV_1% predicted

Covariate	Direction	Effect	*P* value
Baseline FEV_1% predicted	For each 1% increase in baseline FEV_1% predicted	0.69% ± 0.05% increase in longitudinal peak FEV_1% predicted	<.0001
Longitudinal peak BMI%*	For each 1% increase in longitudinal peak BMI%*	0.17% ± 0.05% increase in peak FEV_1% predicted	<.0001
Chronic *P aeruginosa* infection	Yes	4.86% ± 1.89% reduction in peak FEV_1% predicted	.012
Long-term dornase alfa use (> 1 year of use before FEV_1% predicted measurement)	Yes	2.9% ± 1.5% increase in peak FEV_1% predicted	.048

Shown are repeated-measures models with peak FEV_1% predicted from age 6 to 12 years as the dependent outcome variable and significant covariate associations (± standard error of the mean) using the Wang[11] reference equations to calculate peak FEV_1% predicted (n = 144 patients).
*Percentile.

Table IV. Factors associated with peak FEV_1% slope (rate of change)

Covariate	Direction	Effect	*P* value
Baseline FEV_1% predicted	For each 1% increase in baseline FEV_1% predicted	0.08% ± 0.02% increase in rate of decline in peak FEV_1% predicted	<.0001
Baseline BMI%*	For each 1% increase in baseline BMI%*	0.03% ± 0.01% reduction in rate of decline in peak FEV_1% predicted	.017
BMI%* slope (rate of change)	For each unit of increase in peak BMI%* slope	0.28% ± 0.07% reduction in rate of decline in peak FEV_1% predicted	.0003
Chronic *P aeruginosa* infection	Yes	2.1% ± 0.7% increase in rate of decline in peak FEV_1% predicted	.004
Initiation of dornase alfa therapy before age 9 years	Yes	1.6% ± 0.7% reduction in rate of decline in peak FEV_1% predicted	.028

Shown are the results from a linear regression model with peak FEV_1% slope (rate of change) from age 6 to 12 as the dependent outcome variable and significant covariate associations (± standard error of the mean) using the Wang[11] reference equations used to calculate peak FEV_1% predicted (n = 144 patients).
*Percentile.

of decline in lung function in CF have yielded varied findings. Impaired glucose tolerance and diabetes have been associated with a faster decline in lung function.[13,14] Several studies, including ours, found an association between chronic *P aeruginosa* respiratory tract infection and a faster decline in lung function.[14-16] Konstan et al,[16] analyzing CF Foundation Registry data, found associations between sex, nutritional status, hospitalization rates, insurance status, and ibuprofen use and the rate of decline in lung function in children with CF. Corey et al[3] found direct associations between female sex, homozygous Delta F508 genotype, and pancreatic insufficiency and the rate of decline in lung function in CF. Our database did not include adequate data on ibuprofen use, insurance status, or hospitalization rates during the study period for these variables to be included in our models. The patients in our study were predominately homozygous Delta F508 genotype, and nearly all received pancreatic enzyme supplementation. Our sample size was not sufficient to detect small differences in the rate of decline in lung function based on genotype or classification of pancreatic status. We found no differences in the rates of decline in FEV_1% predicted between the male and female patients from age 6 to 12 years. The earlier studies from Konstan et al and Corey et al differ from ours in some important ways; both of those studies included an older cohort of patients and calculated the rate of decline in lung function using Knudson reference equations, which have well-recognized limitations in estimating lung function in children.[17]

Prospective clinical trials of up to 2 years duration have demonstrated improvements in absolute lung function in children with CF receiving dornase alfa therapy.[18,19] Our data span 13 years of clinical dornase alfa use. Peak FEV_1% predicted values obtained at least 1 year after initiation of dornase alfa therapy were 2.9% ± 1.5% higher than all other FEV_1% predicted values, after adjustments for age at diagnosis, age at lung function testing, sex, genotype, baseline FEV_1% predicted, baseline BMI%, yearly peak BMI%, and chronic respiratory tract status. The FEV_1% predicted slope was 1.6% ± 0.7% better in those patients who started dornase alfa before age 9 years compared with those who started after age 9 or who did not use dornase alfa, after adjustments for age at diagnosis, age, sex, genotype, baseline FEV_1% predicted, baseline BMI%, BMI% slope, and chronic respiratory tract infection status.

We report the unique long-term association of earlier initiation of dornase alfa therapy with improvement in the rate of decline in lung function in children with CF. This association does not prove causality, however. There may be

unrecognized and important differences between the families that chose earlier initiation of dornase alfa therapy and the other families that could account for the different rates of decline in lung function between patient groups. These differences may include differences in primary CF caregiver, level of counseling received, insurance status, education level, socioeconomic status, secondhand cigarette smoke exposure, and/or adherence to the CF therapeutic regimen. An analysis of The CF Foundation Registry data is needed to further investigate the association between earlier initiation of dornase alfa therapy and improvement in the rate of decline in lung function in children.

Improvements in absolute lung function and the rate of decline in lung function in our patients with CF are associated with a higher frequency of clinical visits and a lower prevalence of chronic *P aeruginosa* infection. Our findings complement earlier findings from the Epidemiologic Study of Cystic Fibrosis (ESCF). ESCF study sites in the upper quartile for lung function had a greater frequency of clinical visits and a lower prevalence of *P aeruginosa* infections in their infant cohorts compared with centers in the lowest quartile.[20] During the past decade, in our CF center we have improved our infection control standards and focused on early eradication of *P aeruginosa* colonization of the respiratory tract, to decrease the prevalence of chronic *Pseudomonas* infections in our patients.

The association of better nutrition with improved lung function outcomes in children with CF is well established. However, to date no study has demonstrated a causal connection between nutrition and lung function outcomes. Zemel et al[21] analyzed 968 children with CF and pancreatic insufficiency in the National CF Registry and reported associations between baseline height for age *z*-score and weight for age *z*-score with longitudinal changes in FEV_1% predicted. Konstan et al[22] analyzed 931 young children from the ESCF study and reported associations of baseline weight for age%, height for age%, and percent ideal body weight at age 3 years with subsequent FEV_1% predicted at age 6 years. In our patients, both baseline BMI% and BMI% slope were independently associated with the FEV_1% predicted slope, and the yearly peak FEV_1% predicted was associated with the longitudinal BMI%.

Our analysis demonstrates statistically significant improvements in the rates of decline in lung function in patients with CF. This is the first analysis to demonstrate a long-term association of dornase alfa therapy and an improved rate of decline in lung function in patients with CF. In our center, we currently recommend dornase alfa therapy to all patients age 6 years and older, independent of lung function. Dornase alfa also has potential benefits in patients with CF under age 6 years.[23] Our findings should stimulate discussions in the CF community regarding consensus age and lung function criteria for initiating dornase alfa therapy.

Our study is a limited retrospective analysis, and the associations stated herein do not imply causality. The study is limited by its single-center design, and our results may not be reflective of results from other CF centers. Our CF database has some limitations. We were unable to include data collected before 1994 because of inconsistent data entry patterns. We did not have sufficient data to allow us to include hospitalization rates, socioeconomic status, parental education, or secondhand smoke exposure in our models. Our database did not contain information on glucose tolerance testing before 2001; thus, we were unable to include glucose intolerance or CF-related diabetes as covariates in our regression models. We also were unable to include chronic inhaled tobramycin cycles in our regression models, because our database documentation did not distinguish chronic cycles from episodic use.

In conclusion, CF lung function and nutritional outcomes have dramatically improved in our CF center. Patients with CF born between 1993 and 2000 have better initial lung function at age 6 years, better lung function from age 6 to 12, improved rate of decline in lung function from age 6 to 12, and better nutritional outcomes compared with patients born between 1985 and 1992. In our regression model, factors associated with a better FEV_1% predicted slope (rate of decline) from age 6 to 12 years were a higher baseline BMI%, a slower BMI% rate of decline, lack of chronic *P aeruginosa* respiratory tract infection, and initiation of dornase alfa therapy before age 9. The rate of decline in lung function from age 6 to 12 years in our CF center is negligible. The finding of similar results in other CF centers will have implications for the design of outcome measures for future clinical trials of CF lung disease.

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50 Years Ago in *The Journal of Pediatrics*

Empyema in children: A 25-year study

Lionakis BL, Gray SW, Skandalakis JE, and Hopkins WA. J Pediatr 1958;53:719-25

". . .this study covers the period of practical extinction of empyema" and "1947 should mark the essential closing of this chapter of the history of thoracic surgery" are 2 ill-fated prophesies made by these authors based on their observation that the incidence of childhood empyema had fallen dramatically after the introduction of antibiotics in the late 1940s. Contrary to their predictions, however, the worldwide incidence of childhood empyema continues to increase, the reason for which remains unknown. The most common causative organisms remain pneumococcus and staphylococcus; however, there is evidence that pneumococcal serotype 1 is becoming more dominant. This shift in serotype has been speculated to be due to the introduction of a 7-valent pneumococcal vaccine that does not cover serotype 1; however, to date an association, but not a causation, has been shown.

Despite the increase in cases, the outcomes for children with empyema have improved greatly since the time of this report. In the authors' observation period from 1932 to 1957, the average length of hospital stay was 7 weeks, and death occurred in approximately 50% of children under age 2 years. Today, death rarely occurs, and the average hospital stay is less than 1 week after intervention.

Although it has been recognized since Hippocrates' time that drainage of empyema is essential, the best method to do so remains controversial. Rib section, the treatment of choice 50 years ago, has been replaced by primary video-assisted thoracoscopic surgery (VATS), and chest drainage has been refined by the use of small percutaneous drains with instillation of fibrinolytics, which is cheaper than and as effective as VATS. The past 5 decades also have seen the development of imaging techniques to aid diagnosis. Although ultrasound is a useful tool, some children may be receiving unnecessary exposure to radiation from routine computed tomography scans, which may not affect management.[1] We need to be mindful not to do unnecessary harm as we strive to perfect the prevention and treatment of empyema in children over the next 50 years.

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