Pancreatic Enzyme Replacement Therapy Dosing and Nutritional Outcomes in Children with Cystic Fibrosis

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Objectives To utilize the Cystic Fibrosis Foundation Patient Registry to evaluate whether pancreatic enzyme dose is associated with better nutritional status as measured by average body mass index (BMI) percentile.

Study design A retrospective analysis of the Cystic Fibrosis Foundation Patient Registry from 2005-2008 was performed. The final analysis included 42 561 patient visits from 14 482 patients 2-20 years of age taking pancreatic enzyme replacement therapy from 179 programs. Cystic fibrosis care programs were assigned to quartiles based on adjusted mean patient BMI percentiles. Differences in median lipase dose between programs in the highest and lowest BMI quartiles were examined using a mixed effects model that adjusted for individual patient BMI, age, race, ethnicity, forced expiratory volume in 1 second percent, acid-blocker use, presence of *Pseudomonas aeruginosa*, nutritional supplement use, growth hormone use, and diagnosis of cystic fibrosis-related diabetes.

Results A significant difference in median enzyme dose existed between the highest and lowest BMI quartiles. Multivariable analysis demonstrated the effect persisted after adjustment for covariates. Highest quartile programs had a median enzyme dose of 1755 lipase units/kg/meal compared with 1628 lipase units/kg/meal for lowest quartile programs.

Conclusion Patients attending US cystic fibrosis programs achieving highest nutritional outcomes, measured by mean BMI percentile, have higher enzyme dosing than those attending programs at lower performance levels. Further randomized clinical trials are necessary to determine the role of enzyme dose in improving nutritional outcomes. *(J Pediatr 2014;164:1110-5)*.

Cystic fibrosis (CF) is an autosomal recessive disorder that affects approximately 30 000 individuals in the US.[1] One of the hallmark features of CF is pancreatic insufficiency requiring pancreatic enzyme replacement therapy (PERT). According to the 2011 CF Foundation (CFF) Patient Registry Annual Report, 87.4% of individuals with CF are on some form of PERT.[1] Numerous studies demonstrate nutritional status is highly predictive of pulmonary function and survival in CF.[2-7] Furthermore, there is wide variability in CF center nutrition outcomes in the US.[1]

Numerous factors contribute to nutritional status in patients with CF: pancreatic insufficiency and chronic malabsorption, recurrent sinopulmonary infections, chronic inflammation, increased energy expenditure, and suboptimal intake. Even though PERT is an integral part of optimizing nutrition, little published data specifically evaluates the impact of PERT dosing on growth and outcomes in children with CF. The CFF currently recommends that proprietary PERT be provided at a dose no greater than 10 000 lipase units/kilogram/d.[8] This recommendation was developed from a series of case reports and case control studies from the United Kingdom and US suggesting that high dose pancreatic enzyme supplementation was associated with fibrosing colonopathy.[9,10] The premise of the current dosing recommendation is based on providing doses that are unlikely to cause harm rather than those that are most effective. Not surprisingly, wide variation in PERT dosing exists among the US population with CF. For example, in 2010, the range of pancreatic enzyme dosing in children 2-19 years of age was between 1000 and 3000 lipase units/kg/meal with a mean of 1820 lipase units/kg/meal at US CF programs.[1]

To investigate whether pancreatic enzyme dosing might be a determinant of better nutritional status, as measured by average body mass index (BMI) percentile, we undertook a retrospective analysis of the CFF Patient Registry (CF Registry). A center based analysis was used to avoid the problem of indication bias.[11] This approach has been used in a previous analysis of pulmonary outcomes to reflect general practice patterns and to provide a potential basis for quality improvement initiatives.[12,13]

BMI	Body mass index
CF	Cystic Fibrosis
CFF	Cystic Fibrosis Foundation
CF Registry	CFF Patient Registry
FEV1%	Forced expiratory volume in 1 second percent
PERT	Pancreatic enzyme replacement therapy

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Methods

Patients 2-20 years of age taking PERT who were included at anytime in the CF Registry from January 1, 2005-December 31, 2008, were included in this analysis. A description of the CF Registry is published in an annual report by the CFF.[1] Data collected on each patient includes demographics, use of chronic therapies, results of pulmonary function testing, results of respiratory cultures, information on growth and nutrition, and details related to acute changes in management. The CF Registry started recording pancreatic enzyme doses in 2005. This study was reviewed and approved by the CFF Registry Committee and the institutional review board at the Ann and Robert H. Lurie Children's Hospital of Chicago.

Analyses were completed at the patient level as well as aggregated by CF center. Programs with fewer than 10 unique patients on enzyme supplementation were excluded from the center level analyses. Center level BMI percentile performance quartiles were established according to the 2008 mean adjusted BMI percentile from each center, which were provided by the CF Registry. The patient level BMI percentile values used to calculate the mean center level BMI percentile were calculated from the mean of the highest BMI percentile value reported per quarter in the registry. Mean center BMI percentile is case-mix adjusted to account for intrinsic patient and disease characteristics that influence patient outcomes, including average patient age, race/ethnicity, median family income by zip code, age at diagnosis, presentation (meconium ileus, respiratory and gastrointestinal symptoms, respiratory symptoms alone, gastrointestinal symptoms alone, other), and use of pancreatic enzymes.

The pancreatic enzyme replacement dose used for our calculations was the highest reported enzyme dose on any encounter during the year. Individual enzyme dose was compared for all patients at programs within the top and bottom BMI percentile quartiles. Patient and center level characteristics and median center enzyme dose was also compared between top and bottom BMI-percentile performance quartiles.

Demographic and clinical factors that may be confounders associated with nutritional outcomes were determined after a review of the CF literature and considered for inclusion in a multivariable model. These included both static variables, such as age at diagnosis, sex, and race, as well as covariates that vary over time, such as forced expiratory volume in 1 second percent (FEV1%) predicted. Data provided by the CF Registry is adjusted for socioeconomic status, and, therefore, these variables were not further adjusted in our analysis. Center level analysis was aggregated over patients, as proportion of patients with dichotomous characteristics (eg, proportion of patients with nutritionist evaluation) and average of linear characteristics (eg, FEV1%). Static characteristics were compared between bottom and top BMI performance quartiles using t test, χ^2 analysis, or Wilcoxon rank sum test as appropriate. Characteristics that varied over time were compared between lowest and highest quartiles using mixed models with a fixed effect of year and a covariance structure nesting patients within programs, and results are presented as least square means and SEs. In addition, a similar mixed model including patient BMI, age, race, ethnicity, FEV1%, acid-blocker use, presence of *Pseudomonas aeruginosa*, supplemental feed use, growth hormone use, and diagnosis of CF-related diabetes as covariates while still modeling a nested covariance structure with patient within programs was used to assess if any differences in enzyme dose by quartile was still evident after adjusting for these potential confounders; estimated least squared means and SEs are presented. Secondary analyses of enzyme dose by quartile were similarly performed with Centers for Disease Control and Prevention weight for age and Centers for Disease Control and Prevention height for age percentiles substituted for patient BMI percentile.

The trend of enzyme dose within and between all quartiles over time was also examined. As enzyme dose was significantly skewed, medians and quartiles are presented. Both the median of patient doses, as well as the median of programs' doses are presented and compared using Wilcoxon signed rank and Wilcoxon rank sum tests. These results are unadjusted and are presented both as the median of all patients, as well as the median patient level of the programs.

All statistical tests were 2-sided at a type I error rate of 5%. All analyses were performed with SAS v 9.3 (SAS Institute, Cary, North Carolina).

Results

The final analysis included 42 561 patient visits from 14 482 patients from 179 programs. Each quartile ultimately contained 45 programs, with the exception of the lowest quartile, which contained 44 programs. The median (25th, 75th percentile) enzyme dose from the last visit of all patients was 1755 (1329, 2150) lipase units/kg/meal, and the average BMI percentile of all patients was the 45.2 percentile (SD 27.0%). The Spearman correlation coefficient of enzyme dose and BMI percentile was −0.176, which, because of the large sample, was statistically significant ($P < .001$), but not clinically meaningful.

The numbers of patients in the top and bottom BMI quartiles were 3475 and 3205, respectively. Several statistically significant differences exist between the patient characteristics of lowest and highest quartile programs (**Table I**). Patients at top quartile programs were younger, despite not showing a statistically significant difference in age at diagnosis. Top quartile programs had fewer patients diagnosed by electrolyte imbalance, failure to thrive/malnutrition, meconium ileus, and steatorrhea. Furthermore, programs with best BMI performance had more patients diagnosed by way of newborn screening and demonstrated higher lung function as measured by FEV1% predicted, forced vital capacity percent predicted, and FEV1%/forced vital capacity percent. Top quartile and