Gastric Acid Inhibition for Fat Malabsorption or Gastroesophageal Reflux Disease in Cystic Fibrosis: Longitudinal Effect on Bacterial Colonization and Pulmonary Function

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Objectives To investigate bacterial colonization and pulmonary function longitudinally in patients with cystic fibrosis (CF) receiving drugs for gastric acid (GA) inhibition for fat malabsorption or for gastroesophageal reflux disease (GERD).

Study design A retrospective cohort study of 218 pediatric patients with CF was performed. Multilevel modeling was used to perform longitudinal analysis of forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), maximum expiratory flow at 50% of FVC (MEF_{50}), and maximal mid-expiratory flow between 25% and 75% of FVC ($MMEF_{25-75}$). Cox regression was used to calculate *Pseudomonas aeruginosa*- and *Staphylococcus aureus*-free survival.

Results Patients with CF and GA inhibition had a significantly smaller yearly decline of MEF_{50} and $MMEF_{25-75}$ compared with control subjects. Other pulmonary function parameters and *P aeruginosa* or *S aureus* acquisition or colonization were not different from that of control subjects. GERD was associated with a significantly reduced pulmonary function (FEV_1 and FVC) and an earlier acquisition of *P aeruginosa* and *S aureus*.

Conclusions GA inhibition did not affect pulmonary function or bacterial acquisition and therefore is not contraindicated in patients with CF. GA inhibition might improve pulmonary function with time, because the decline of MEF_{50} and $MMEF_{25-75}$ was less pronounced. GERD was associated with a reduced pulmonary function and an earlier acquisition of *P aeruginosa* and *S aureus*. Therefore the diagnosis and treatment of GERD should be aggressively pursued in patients with CF. *(J Pediatr 2009;155:629-33)*.

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Most patients with cystic fibrosis (CF) have exocrine pancreatic insufficiency, which is treated with pancreas enzyme replacement therapy. Gastric acid (GA) inhibition via proton pump inhibitors or histamine-2 receptor antagonists is added when fat absorption remains insufficient despite an adequate dosage of pancreas enzyme replacement.[1,2] Gastroesophageal reflux disease (GERD) is another reason to start drugs for GA inhibition in patients with CF.

In various populations without CF, GA inhibition has been shown to be associated with an increased risk for pulmonary infections (eg, intensive care patients treated with histamine-2 antagonists for the prevention of stress ulcers have an increased risk of pneumonia[3] and more recently, an increased risk for community-acquired pneumonia has been reported in both pediatric patients with GERD and adult patients receiving GA inhibition for various reasons).[4,5]

The effect of GA inhibition on pulmonary function in patients with CF is unclear; cross-sectional analysis showed that GA inhibition for GERD in patients with CF is associated with a reduced forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC),[6,7] and FEV_1, FVC, and maximum expiratory flow at 50% of FVC (MEF_{50}) did not change during 1 year of GA inhibition treatment in a small study of patients with CF with fat malabsorption.[8]

BMI	Body mass index
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane regulator
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GA	Gastric acid
GERD	Gastroesophageal reflux disease
MEF_{50}	Maximum expiratory flow at 50% of FVC
$MMEF_{25-75}$	Maximal mid-expiratory flow between 25% and 75% of FVC
OR	Odds ratio
PA	*Pseudomonas aeruginosa*
SA	*Staphylococcus aureus*

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Therefore the aim of this study was to longitudinally investigate pulmonary function and bacterial colonization in a large cohort of pediatric patients with CF who were receiving drugs for GA inhibition for either fat malabsorption or GERD.

Methods

A retrospective cohort study of all pediatric patients with CF (age ≤18 years) treated in the CF Center of the University Medical Center Utrecht on January 1, 2007, was performed according to the guidelines of the medical ethics board of the University Medical Center Utrecht.

Patients were classified in 3 groups on the basis of the history of GA inhibition (proton pump inhibitors or histamine-2 receptor antagonists). The first group consisted of patients receiving GA inhibition because of insufficient effect of pancreas enzyme replacement therapy (fat absorption coefficient <85%, with impaired growth or weight gain). The second group used GA inhibition for GERD, defined as abnormal results of 24-hour esophageal pH monitoring or esophagitis on esophageal histology.[9] The performance of esophageal pH monitoring or esophageal endoscopy was indicated on the basis of clinical signs of gastroesophageal reflux. The third group had no history of GA inhibition (control subjects). Patients for whom the indication for GA inhibition could not be retrieved were excluded. In the subsequent analysis, these clinical characteristics were analyzed: sex, current age, age at diagnosis of CF, cystic fibrosis transmembrane regulator (CFTR) genotype severity, lower airway culture results (especially *Pseudomonas aeruginosa* [PA] or *Staphylococcus aureus* [SA]), presence of meconium ileus at birth, distal intestinal obstruction syndrome, and liver cirrhosis.

All pulmonary function tests and body mass index (BMI) z-scores from the first visit at the CF center were retrieved. Patients with at least 2 pulmonary function measurements were included in the longitudinal analysis. Pulmonary function assessments and BMI z-scores of patients with GERD or patients with fat malabsorption during GA inhibition treatment were compared with the pulmonary function tests of patients without a history of GA inhibition.

Pulmonary function (FEV_1, FVC, MEF_{50}, $MMEF_{25-75}$) was measured with spirometry and converted to percentage of predicted values.[10] Patients with at least 1 PA- and SA-positive culture test (ever) were identified, and the date of the first positive culture test was determined. Patients were considered to be colonized with PA or SA when the monthly culture test results (sputum or cough swab) in a 3-year period were ≥50% positive.[11] Patients with <2 culture tests were excluded. Patients with 2 severe CFTR mutations (class I-III) were considered to have a severe CFTR genotype.[12] Distal intestinal obstruction syndrome was defined according the ESPGHAN CF Working Group criteria.[13] Patients with a nodular liver margin on ultrasound scanning were classified as having cirrhosis.

Statistical Analysis

Categorical variables were analyzed with the Pearson χ^2 or Fisher exact test, and continuous variables were analyzed with the Mann-Whitney *U* test. Logistic regression was used to determine risk factors for GERD or fat malabsorption requiring GA inhibition. Cox regression analysis was used to analyze the effect of the treatment groups on PA- and SA-free survival.

Multilevel linear regression modeling was used to perform longitudinal analysis of pulmonary function and nutritional status (BMI z-score), because it allows inclusion of variable numbers of measurements per child and adjusts for irregularly timed and missing observations.[14-16] In this model, yearly decline of pulmonary function and nutritional status and intercept at 10 years of age were compared in the 3 treatment groups, and adjustments for confounders (sex, age, severe CFTR genotype, PA and SA colonization, BMI z-score for pulmonary function, FEV_1 for nutritional status) were made. Also, when necessary, adjustments were made for the remaining variables (age at diagnosis of CF, meconium ileus, distal intestinal obstruction syndrome, cirrhosis).[15,16] For the longitudinal analysis of pulmonary function intercept, age

Table I. Baseline characteristics of patients receiving gastric acid inhibition for fat malabsorption, gastroesophageal reflux disease, and patients without a history of gastric acid inhibition (control subjects)

Characteristics	Fat malabsorption	GERD	Controls	*P* value*	OR (95% CI)	*P* value†	OR (95% CI)
Number	79	12	127				
Sex (male)	46 (58%)	6 (50%)	67 (53%)	.44	1.2 (0.7; 2.2)	.86	0.90 (0.27; 2.9)
Current age (years)‡	10.0 (4.4)	7.1 (4.9)	10.2 (4.6)	.64	0.99 (0.93; 1.1)	.036	0.87 (0.76; 0.99)
Age at diagnosis of CF (years)‡	0.7 (1.4)	0.7 (1.4)	1.5 (2.2)	.001	0.76 (0.62; 0.93)	.07	0.72 (0.42; 1.2)
Severe CFTR genotype	71 (90%)	11 (92%)	96 (76%)	.011	2.8 (1.2; 6.6)	.30	3.6 (0.44; 28.6)
Meconium ileus	11 (14%)	5 (42%)	13 (10%)	.42	1.4 (0.60; 3.3)	.009	6.3 (1.7; 22.6)
Distal intestinal obstruction syndrome	8 (10%)	1 (8%)	6 (5%)	.13	2.3 (0.76; 6.8)	.48	1.8 (0.20; 16.6)
Cirrhosis	12 (15%)	1 (8%)	9 (7%)	.06	2.3 (0.94; 5.9)	1.00	1.2 (0.14; 10.3)
Ever PA positive	50 (65%)	10 (83%)	91 (75%)	.12	0.61 (0.33; 1.1)	.73	1.6 (0.34; 7.9)
PA colonization	18 (23%)	3 (25%)	32 (26%)	.63	0.85 (0.44; 1.6)	1.00	0.93 (0.24; 3.6)
Ever SA positive	72 (94%)	10 (83%)	115 (95%)	.75	0.75 (0.22; 2.6)	.15	0.26 (0.05; 1.5)
SA colonization	37 (48%)	5 (42%)	65 (54%)	.44	0.80 (0.45; 1.4)	.43	0.62 (0.19; 2.0)

*Fat malabsorption versus control subjects.
†GERD versus control subjects.
‡Mean (SD).