Cystic Fibrosis and Sinusitis in Children: Outcomes and Socioeconomic Status

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Abstract

Objectives. Although chronic sinusitis is prevalent in children with cystic fibrosis (CF), little is known regarding pulmonary outcomes following endoscopic sinus surgery (ESS). Furthermore, lower socioeconomic status (SES) is associated with increased morbidity in children with CF. The investigators evaluated the impact of surgery and SES on pulmonary function tests (PFTs) in children with CF and rhinosinusitis.

Study Design. Longitudinal, retrospective cohort study.

Setting. Urban tertiary CF center.

Subjects and Methods. Children with CF ages 0 to 21 evaluated for sinusitis between 1998 and 2008 were analyzed. Children were grouped according to surgery status (ESS or no ESS). Medicaid (MA) insurance was used as a proxy for lower SES. PFTs (percent predicted forced vital capacity [FVC%predicted] and percent predicted forced expiratory volume in 1 second [FEV1%predicted]) were recorded over 2 years. Multivariate linear regression models and interaction terms (ESS and MA) were used to analyze PFTs.

Results. Of 62 patients evaluated, 21 (34%) underwent ESS, and 16 (26%) had MA. Polyps were more common in the ESS group (86% vs 32%, \( P < .001 \)). FEV1%predicted and FVC%predicted were lower at all times for children with MA \( (P < .001) \). After adjustment for MA, mean FEV1%predicted was higher for the ESS group at all time points \( (P < .02) \), and mean FVC%predicted was higher at 1 and 2 years \( (P = .02, P = .01) \). Compared with the nonsurgical group, children without MA undergoing ESS had higher mean FEV1%predicted at all 3 follow-up visits \( (P \leq .05) \). Children with MA who underwent ESS had higher mean FVC%predicted at 1 year \( (P = .04) \) and higher mean FEV1%predicted preoperatively and at 1 year \( (P \leq .01) \).

Conclusions. Children with CF and sinusitis who undergo ESS experience some increase in PFTs over time, although this change is not uniform. Children with CF and sinusitis who are from lower socioeconomic backgrounds have lower PFTs over time regardless of surgical intervention.

Keywords
cystic fibrosis, pediatric rhinosinusitis, socioeconomic status, outcomes research

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Cystic fibrosis (CF) affects approximately 1 in 3500 newborns, making it the most common life-threatening autosomal recessive genetic disorder in the United States.\(^1\) Gene mutations in the CFTR gene on chromosome 7 disrupt cAMP-mediated chloride secretion in epithelial cells lining the airways and exocrine glands.\(^2\)–\(^4\) There is increased viscosity of secretions resulting in bronchiectasis, pancreatic insufficiency, secondary infections, and sinonasal polyposis. Although the major concerns of CF are airway infections and malabsorption, up to 100% of patients display chronic rhinosinusitis and up to 50% have nasal polyps.\(^5\)

The degree to which sinus disease contributes to decline of lung function in children with CF is largely unknown, although sinusitis may have more of an impact than previously appreciated. The severity of sinusitis has been correlated with the severity of pulmonary disease in children with CF based on pulmonary function tests.\(^6\) In CF, the CFTR defect almost universally causes inflammation of upper airway mucosa, leading to frequent complaints of nasal obstruction and nasal discharge.\(^7\) When conservative approaches such as nasal corticosteroids and/or antibiotics

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to manage chronic rhinosinusitis fail, endoscopic sinus surgery (ESS) is recommended for children and adults with CF. While ESS has not been shown to reduce hospitalizations for children with CF, it has been demonstrated to improve quality of life, decrease nasal symptoms, and improve secondary symptoms such as activity level.\textsuperscript{8,9} Although not explored in children, adults with CF gain similar degrees of improvement after ESS compared with adults without CF, even though sinus disease severity was significantly worse.\textsuperscript{10} Unfortunately, there is limited evidence-based information regarding long-term pulmonary function in children with CF and rhinosinusitis or any specifics as to how ESS affects these clinical outcomes.

Although treatment advances have been substantial and many CF patients survive into adulthood, the course of CF remains heterogeneous and the variability is incompletely explained. Socioeconomic status (SES) has been shown to be an important predictor of outcomes in many chronic diseases, such as diabetes, obesity, and asthma. Several studies suggest that SES may also predict outcomes in CF, as patients with lower SES in both the United Kingdom and United States have poorer outcomes and decreased survival.\textsuperscript{11-13} Studies have shown that children with CF and disadvantaged SES have decreased lung function, height, weight, and overall survival.\textsuperscript{3,14}

While low SES has been associated with increased mortality in children with CF, little is known regarding SES or pulmonary outcomes in children with CF and rhinosinusitis. Our objectives were to (1) evaluate SES and long-term pulmonary function in children with CF and rhinosinusitis and (2) assess the association of endoscopic sinus surgery (ESS) with these outcomes.

**Methods**

This study received approval by The Johns Hopkins Institutional Review Board (NA_00035062). Patients were included if they were age 0 to 21 with CF and rhinosinusitis seen at the Johns Hopkins Hospital Cystic Fibrosis center from November 1, 1998, to November 1, 2008, and part of the National Cystic Fibrosis Foundation Registry. Otolaryngology physician billing records were queried to identify CF patients with the diagnosis of chronic sinusitis \textit{(International Classification of Diseases, 9th Revision Clinical Modification codes 277 and 473)}. All patients were seen in the otolaryngology clinic for sinusitis, and the children were grouped according to management with or without surgery (ESS or no ESS). Children were also categorized according to SES. Medicaid insurance coverage (MA) was used as a proxy variable for low SES based on previous studies.\textsuperscript{14} A correlation analysis between income class (greater than or less than $60,000 per year, based on mean for zipcode), median annual income, and presence of MA was performed, showing a 30% to 40% correlation. To account for the impact of SES on PFTs, in addition to MA, income class was included as a possible confounding variable in the adjusted regression models. Demographic characteristics were collected through the CF registry.

To track pulmonary status, the age-specific percent predicted forced expiratory volume in 1 second (FEV\textsubscript{1}) and forced vital capacity (FVC) were collected for all of the patients. FEV\textsubscript{1}%predicted and FVC%predicted are pulmonary function tests (PFTs) commonly used as markers of overall pulmonary status and to track the progression and severity of CF.\textsuperscript{1} PFTs at several time points were recorded. The first measurement represented preoperative status for those undergoing ESS or the first otolaryngology encounter for children who did not undergo surgery. Measurements were also obtained at 6-month, 1-year, and 2-year intervals following ESS or the first otolaryngology encounter for the non-ESS group. Unadjusted values were collected, and change scores (or difference scores, Y – X) between the initial encounter and the 3 subsequent time points were calculated. Age-specific body mass index was recorded.

Multivariate linear regression models with generalized estimating equations were used to analyze PFT measurements at all 4 study visits. Exchangeable working correlation was assumed for the within-person correlation to account for the correlation between observations taken on the same individual. Regression models were performed to compare unadjusted differences in mean PFTs as well as change scores between the ESS and non-ESS groups. To consider the effect modification among visits, MA and ESS, we used interaction terms in the regression models, which stratify the study population into 4 strata—non-ESS and non-MA, non-ESS and MA, ESS and non-MA, ESS and MA—at all time points, adjusting for age, gender, and income class. Linear combinations of the model estimates were used to determine the group means and differences between groups. Statistical significance in this study is reported as $P$ values and 95% confidence intervals (CIs). Given the multiple comparisons, a more stringent $P$ value was considered to reduce type I error, or false assumption of a true difference; however, it was deemed too conservative for this exploratory analysis. Therefore, a $P$ value of less than .05 was considered significant. Data analysis was performed using Stata version 11.0 (Stata Statistical Software; College Station, Texas).

**Results**

Of 62 patients evaluated, 21 (34%) underwent ESS, and 16 (27%) had MA. Age at evaluation and gender were similar regardless of MA status or ESS. Polyps were more common in the ESS group (86% vs 34%, $P < .001$). The most common genotype was homozygote \textit{ΔF508} (50%). There was no significant difference in the distribution of mutations between the ESS and non-ESS patients. Patient demographics are detailed in Table 1.

Table 2 shows the mean values of PFTs after adjustment for MA, gender, median annual income, and age at initial encounter, whereas Table 3 shows the difference in PFTs before and after adjustment. The ESS group had higher mean FEV\textsubscript{1}%predicted and FVC%predicted at baseline; however, this difference was not significant. For FEV\textsubscript{1}%predicted, the difference between ESS and non-ESS
was significant at all time points after adjustment. Figure 1 shows the adjusted mean PFTs for the ESS and non-ESS groups. All mean values of FVC%predicted were higher for the ESS group, but this only achieved significance at 1 year and 2 years postoperatively when compared with the non-ESS group.

Change scores for PFTs in each group were calculated from the initial visit to follow-up visits, and these showed little difference before and after adjustment for MA. Table 4 shows the unadjusted and adjusted change scores for mean PFTs, separated by ESS and non-ESS. Table 5 shows the comparison of change scores between ESS and non-ESS.
non-ESS. This table showed that the difference in the change in FVC% was marginally higher (adjusted 5.4, \( P = .055 \)) at 2 years between ESS and non-ESS patients. For FEV1\% predicted, the changes were always higher but not significant for any of the 3 follow-up visits.

The results of the multivariate regression analysis with interaction terms for ESS and MA at all time points are shown in Figure 2 (FVC% predicted) and Figure 3 (FEV1\% predicted). Both MA groups, non-ESS and ESS, had significantly lower baseline and follow-up PFTs compared with the non-MA groups. At baseline and the 1-year follow-up, the children with MA in the ESS group had significantly higher FEV1\% predicted, whereas FVC% predicted was higher only at 1 year. This improvement was not seen for the MA groups at the 2-year follow-up visit. For the non-MA patients, the baseline PFTs were not significantly

### Table 3. FVC% predicted and FEV1% predicted: Comparison Between Endoscopic Sinus Surgery (ESS) and Non-ESS Groups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Comparison</th>
<th>Time Frame</th>
<th>Unadjusted Estimated Difference</th>
<th>95% CI</th>
<th>P Value</th>
<th>Adjusted Estimated Difference</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC% predicted</td>
<td>ESS vs non-ESS</td>
<td>First encounter</td>
<td>4.7</td>
<td>-6.8 to 16.1</td>
<td>.423</td>
<td>6.7</td>
<td>-2.5 to 15.9</td>
<td>.153</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 mo</td>
<td>2.8</td>
<td>-10.5 to 16</td>
<td>.680</td>
<td>4.6</td>
<td>-6.5 to 15.6</td>
<td>.418</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 y</td>
<td>8.8</td>
<td>-2.8 to 20.5</td>
<td>.138</td>
<td>10.8</td>
<td>1.4 to 20.2</td>
<td>.024</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 y</td>
<td>10.2</td>
<td>-1.7 to 22.1</td>
<td>.093</td>
<td>12.1</td>
<td>2.6 to 21.7</td>
<td>.013</td>
</tr>
<tr>
<td>FEV1% predicted</td>
<td>ESS vs non-ESS</td>
<td>First encounter</td>
<td>11</td>
<td>-2.8 to 24.8</td>
<td>.117</td>
<td>12.5</td>
<td>2.1 to 22.9</td>
<td>.019</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 mo</td>
<td>13.3</td>
<td>-2 to 28.6</td>
<td>.089</td>
<td>14.4</td>
<td>2.9 to 26</td>
<td>.014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 y</td>
<td>14.8</td>
<td>0.7 to 28.9</td>
<td>.040</td>
<td>16.1</td>
<td>5.5 to 26.8</td>
<td>.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 y</td>
<td>14.1</td>
<td>-1.4 to 29.6</td>
<td>.074</td>
<td>15.4</td>
<td>4.8 to 26</td>
<td>.005</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.
different, but the ESS group demonstrated increased FEV1%predicted at all follow-up visits ($P < .05$) and increased FVC%predicted at 2 years ($P = .02$). This improvement over the non-ESS group also increased over time, so that the greatest difference was seen at 2 years.

**Discussion**

This study shows that ESS is associated with long-term improvement in PFTs for children with CF and sinusitis. Furthermore, children with MA have globally lower PFTs, but the children who undergo ESS show a trend toward improvement at long-term follow-up compared with those who do not have surgery.

The relationship of sinusitis to CF in children has been previously explored. Children with CF have a 3-fold increase in prevalence of sinus disease compared with the general population, with symptoms including daily headache, chronic cough, and purulent rhinorrhea. Sinus CT imaging of children with CF may reveal hypoplasia of the frontal sinuses, opacification of the maxillary sinuses, and nasal polyposis. Correlation between sinus disease and lower respiratory tract conditions such as asthma and chronic obstructive pulmonary disease has been demonstrated previously. The unified airway model describes the entire respiratory system as an integrated unit, from the nose to the distal bronchioles. The histologic appearance of nasal and bronchial mucosa is similar, and there is evidence that treating upper airway disease leads to improvement in lower airway disease. Specifically, resolution of rhinosinusitis leads to improvement in asthma, including pulmonary function tests and symptom scores. In CF, several studies have shown that sinusitis is a risk factor for decline in FEV1, and the severity of sinus disease correlates with the severity of pulmonary disease in children.

Certainly, the treatment of sinusitis in children with CF is challenging and often not straightforward. Initially, conservative therapy is favored, with sinus irrigations, mucolytics, and topical or systemic corticosteroids and antibiotics as the mainstays of treatment. Antibiotics, such as topical tobramycin, are effective at reducing symptoms and improving endoscopic findings in both acute and chronic

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### Table 4. Change Scores in Pulmonary Function Tests

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group</th>
<th>Time Frame Compared with First Encounter</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Estimated Change</td>
<td>95% CI</td>
<td>$P$ Value</td>
</tr>
<tr>
<td>FVC%</td>
<td>Non-ESS</td>
<td>6 mo</td>
<td>2.5</td>
<td>$-2.4$ to $7.4$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 y</td>
<td>$-3.1$</td>
<td>$-7.3$ to $1.1$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 y</td>
<td>$-0.4$</td>
<td>$-4.2$ to $3.2$</td>
</tr>
<tr>
<td></td>
<td>ESS</td>
<td>6 mo</td>
<td>0.6</td>
<td>$-4.5$ to $5.6$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 y</td>
<td>1</td>
<td>$-4.4$ to $6.4$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 y</td>
<td>5.1</td>
<td>$0.9$ to $9.8$</td>
</tr>
<tr>
<td>FEV1%</td>
<td>Non-ESS</td>
<td>6 mo</td>
<td>$-0.9$</td>
<td>$-4.8$ to $3.1$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 y</td>
<td>$-4.7$</td>
<td>$-8.8$ to $-0.6$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 y</td>
<td>$-0.4$</td>
<td>$-4.7$ to $3.8$</td>
</tr>
<tr>
<td></td>
<td>ESS</td>
<td>6 mo</td>
<td>1.4</td>
<td>$-4.9$ to $7.8$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 y</td>
<td>$-0.9$</td>
<td>$-7.4$ to $5.5$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 y</td>
<td>2.7</td>
<td>$-2.8$ to $8.2$</td>
</tr>
</tbody>
</table>

Abbreviations: ESS, endoscopic sinus surgery; FEV1%predicted, percent forced expiratory volume in 1 second; FVC%predicted, percent forced vital capacity.

### Table 5. Comparison in Pulmonary Function Test Change Scores by Endoscopic Sinus Surgery (ESS) Status

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Comparison</th>
<th>Time Frame Compared with First Encounter</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Estimated Difference</td>
<td>95% CI</td>
<td>$P$ Value</td>
</tr>
<tr>
<td>FVC%</td>
<td>ESS vs non-ESS</td>
<td>6 mo</td>
<td>$-1.9$</td>
<td>$-8.9$ to $5.1$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 y</td>
<td>4.2</td>
<td>$-2.7$ to $11$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 y</td>
<td>5.5</td>
<td>$0$ to $11$</td>
</tr>
<tr>
<td>FEV1%</td>
<td>ESS vs non-ESS</td>
<td>6 mo</td>
<td>2.3</td>
<td>$-5.2$ to $9.8$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 y</td>
<td>3.7</td>
<td>$-3.9$ to $11.4$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 y</td>
<td>3.1</td>
<td>$-3.9$ to $10.1$</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; FEV1%predicted, percent forced expiratory volume in 1 second; FVC%predicted, percent forced vital capacity.
Sinusitis. Topical antibiotics are often used to reduce adverse effects and achieve higher drug concentrations at the target site.

Children with persistent nasal obstruction or refractory sinus symptoms associated with chronic sinusitis who fail medical management are often referred for ESS. Although some studies of ESS in individuals with CF have demonstrated no change in objective outcomes such as pulmonary function or frequency of hospitalizations, many have shown improvement in quality of life and clinical symptoms in both children and adults. Complete remission after ESS is infrequently achieved, mainly due to polyp or disease recurrence. One study of 23 children with CF showed that the median interval between revision sinus surgery was 4 years. A more aggressive surgical approach, even in patients with refractory disease and multiple ESS revisions, was shown to improve pulmonary function and decrease hospital admissions in 15 CF patients during the 6-month postoperative period.

In our study, some longitudinal improvement in PFTs for children with CF who undergo ESS was observed. This improvement seen the first 2 years postoperatively is hypothesized to be attributable to reduction in airway obstruction as well as increased activity level. Sinusitis and nasal polyps tend to return, with the majority of patients experiencing recurrence within 2 to 4 years, so longer follow-up may have shown decreasing PFTs for both medically and surgically managed children. Although improvements in mean PFTs and PFT change scores were not uniformly observed, there was an overall trend toward improvement that may have been clearer with the inclusion of more patients or with a longer period of observation. Furthermore, the mean PFTs for patients who underwent ESS were generally higher compared with the mean PFTs for the nonsurgical patients. It is possible that our conclusions are limited in that patients who underwent ESS may have been better surgical candidates, indicating an improved health status at baseline.

A primary objective of our study was to explore the association of SES and outcomes in children with CF and sinusitis. At each time point, patients with MA had lower PFTs, although there was no difference in number of appointments or surgical operations. SES was the major confounding variable studied because of its well-established correlation with increased morbidity in children with CF. Curtis et al showed no difference in overall survival between patients...
insured privately versus by MA, but longer survival was associated with the presence of any health insurance (private or MA) as well as higher SES. A cohort study of more than 20,000 CF patients used MA as a marker of low SES and demonstrated that MA patients had more than 3-fold increased risk of death as well as lower FEV₁ and weight percentiles. The differences seen in the MA patients were not explained by barriers to specialty health care, because there was no difference in clinic visits between the 2 groups. O’Connor et al showed that lower median household income led to decreased FEV₁ and body weight, and these changes persisted from childhood into adulthood.

This study had several limitations that should be discussed. First, it is a retrospective study, so the sample of children studied was not random and the small number of children included in the study may limit the validity of our findings. Given limitations in data collection, the study does not account for severity of sinusitis or CF based on objective CT scoring, symptoms, or pancreatic enzyme supplementation or pancreatic status, and therefore the baseline severity of sinusitis or CF between groups may have differed. In that regard, compliance with adjunctive medical management for either sinusitis or CF was not assessed, nor was bacteriology of infection, both of which may have affected the overall disease burden. Furthermore, because of the retrospective design, children could not be randomized as to who received surgery, and thus the probability of selection bias regarding who elected for ESS is large and limits conclusions regarding the benefits of surgery in comparison to one group or another. Next, the results of this study showed a trend toward improvement in PFTs during the first 2 years after surgery. Although we included 3 time points up to 2 years postoperatively, longer follow-up may have exhibited a greater difference in outcomes. Additionally, this study included patients treated from 1998 until 2008, and many advances in treatment were made during that time period. Finally, a more comprehensive study of outcomes could improve analysis of the impact of surgery or SES on outcome measures such as frequency of treatment with antibiotics, disease-specific quality of life, or number of hospital admissions in addition to PFTs.

Despite these limitations, this study observed that children with CF and sinusitis who undergo ESS experience improvement in PFTs over time compared with children who do not undergo ESS. Furthermore, although low SES is correlated with lower PFTs throughout time,
children with CF and sinusitis from lower socioeconomic backgrounds who undergo ESS may experience a bigger improvement in postoperative pulmonary outcomes. This finding bears public health significance in that physicians should have heightened awareness of the potential benefits of ESS for children with CF and sinusitis who are from lower socioeconomic strata. Future prospective studies should evaluate multidimensional outcome measures to understand the influence of ESS and SES on children with CF and sinusitis.

Conclusions

Children with CF and sinusitis who undergo ESS experience some improvement in PFTs postoperatively regardless of SES. Children with lower SES have decreased mean PFTs compared with children with higher SES. Surgery for children with CF and sinusitis with higher SES may have a more profound effect on pulmonary outcomes; however, baseline disease severity and health status may affect this finding.

Author Contributions

Lara C. Kovell, first author; Jiangxia Wang, statistician, project design; Stacey L. Ishman, study design, preliminary statistical design and methods, critical review and drafting of manuscript; Pamela L. Zeitlin, study design, primary advisor for Cystic Fibrosis clinic, critical review and drafting of manuscript; Emily F. Boss, principal investigator and senior author.

Disclosures

Competing interests: Stacey L. Ishman, FirstLine Medical: contractor; Pamela L. Zeitlin, Inspire Pharmaceuticals, Medical Advisory Board; patent for sweat rate test for cystic fibrosis, royalty agreement for CF cell lines; clinical trial contracts with PTC Corp, Bayer, Merck (study drug only).

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