Children With Cystic Fibrosis

Who Should Visit the Otorhinolaryngologist?

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Background: Sinonasal complications are common in children with cystic fibrosis (CF). Generally, those children with persistent symptoms of sinonasal polyposis are referred to an otorhinolaryngologic (ORL) physician for sinus surgery. Several studies have reported differences in clinical characteristics between CF patients with and without sinonasal polyps.

Objectives: To predict the presence of sinonasal polyposis in children with CF on the basis of symptoms and clinical characteristics and so to select those children who might benefit from referral to an ORL physician.

Design, Setting, and Patients: Survey of data from a database on the results of yearly multidisciplinary examinations of 140 children with CF.

Main Outcome Measure: Presence of sinonasal polyposis.

Results: In the total population of 140 children, no combination of ORL symptoms and clinical characteristics could accurately predict the presence of sinonasal polyposis. In a subgroup of 73 children with a history of nasal symptoms, independent predictors for the presence of sinonasal polyposis were male sex, age 10 years or older, presence of rhinorrhea, and a forced vital capacity 70% or more of the predicted value. The area under the receiver operating characteristic curve of a scoring rule including these independent predictors was 0.77. The positive and negative predictive values of this rule were 0.86 and 0.71, respectively.

Conclusion: A scoring rule including the independent predictors sex, age, symptoms of rhinorrhea, and forced vital capacity values could reasonably classify children with CF and nasal symptoms into a category with increased risk for sinonasal polyposis, thus facilitating the decision on ORL referral.

The Cystic Fibrosis Center Utrecht of the Wilhelmina Children’s Hospital (Utrecht, the Netherlands) treats children with CF from the central Netherlands. All children 4 years or older undergo a routine yearly multidisciplinary examination regardless of their health status. Since October 1998, all results have been routinely recorded in an electronic database. The ORL evaluation was completed in 140 patients (71 boys, 69 girls), with a mean (SD) age of 11.2 (4.0) years. Nasal polyposis and bulging of the lateral nasal wall were found in 56 (40%) and 27 (19%) children, respectively. Nasal polyposis and/or bulging of the lateral nasal wall, indicative of sinonasal polyposis, were present in 70 patients (50%).

Table 1 summarizes the results of the univariate logistic regression analysis of ORL symptoms and clinical variables for the presence of sinonasal polyposis. Significant predictors ($P < .15$) were male sex; symptoms of rhinorrhea and postnasal drip; high FEV$_1$, FVC, and PEF values; and low CRP levels.

After stepwise multivariate analysis of these parameters, independent predictors for the presence of sinonasal polyposis were symptoms of rhinorrhea and FVC values 70% or greater of the predicted value (Table 2). This predictive model was not reliable (goodness of fit, $P < .004$), and the discriminatory power of the model was poor (ROC area of 0.66).

The association between the presence or absence of sinonasal polyposis and symptoms and clinical characteristics was quantified using univariate logistic regression analysis. Subsequently, predictors that were univariately associated with the outcome (odds ratios with $P < .15$) were included in stepwise fashion according to the ease and frequency with which they are obtained in clinical practice in a multivariate logistic regression model to evaluate their independent value in the prediction of sinonasal polyposis. Predictors from the model with P values greater than .10 were excluded such that a reduced model was derived that included independent predictors of sinonasal polyposis. The selected variables were dichotomized when necessary. Reliability (goodness of fit) of the models was estimated using the Hosmer-Lemeshow test. The prognostic capacity to discriminate between patients with and without sinonasal polyposis was estimated using the area under the receiver operating characteristic curve (ROC area). An ROC area of 1.0 corresponds to a model that perfectly predicts sinonasal polyposis; an ROC area of 0.5 corresponds to a model with random predictive accuracy.

To estimate the prognostic capacity of the final model in other groups of similar patients, the model was validated by random bootstrapping techniques. The final model was transformed into a scoring rule by dividing the regression coefficients of the included predictors by the smallest one and rounding them subsequently to the nearest integer. A total risk score was computed for each patient by assigning points for each predictor present. Predictive values for each category of the scores were calculated.

### RESULTS

The ORL evaluation was completed in 140 patients (71 boys, 69 girls), with a mean (SD) age of 11.2 (4.0) years. Nasal polyposis and bulging of the lateral nasal wall were found in 56 (40%) and 27 (19%) children, respectively. Nasal polyposis and/or bulging of the lateral nasal wall, indicative of sinonasal polyposis, were present in 70 patients (50%).

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This cross-sectional analysis of an unselected population of children with CF demonstrated a high prevalence of sinonasal polyposis (50%). Significant univariate predictors for the presence of sinonasal polyposis were male sex, older age, symptomatic rhinorrhea, good pulmonary function, and low CRP levels. Although in the unselected study population the presence or absence of sinonasal polyps could not be accurately predicted by a combination of these univariate predictors, in the symptomatic population, male sex, age 10 years or older, rhinorrhea, and FVC values 70% or greater of predicted value were significant predictors in a multivariate regression model.

Our study is the only series to include children only. Recent studies in children and adults with CF have reported prevalences of nasal polyposis ranging from 32% to 45%, similar to the prevalence of nasal polyposis found in our population (40%). Also, the prevalence of sinonasal polyposis (nasal polyps and/or bulging of the lateral nasal wall) of 48% and 37% found in other studies was similar to the prevalence in our population (50%).

Only 41 (59%) of the 70 patients with sinonasal polyposis reported one or more ORL symptoms (Table 1). This is consistent with other studies, suggesting that children with CF underreport their symptoms. This could be explained by the congenital nature of their disease, the lack of a healthy baseline status for comparison, and adaptation to their symptoms.

According to the literature, the most frequent symptoms in children with polyposis are rhinorrhea and nasal obstruction. In our population, the most commonly encountered symptoms in patients with sinonasal polyposis were rhinorrhea (36%), postnasal drip (29%), and nasal obstruction (27%). Of these symptoms, only rhinorrhea was a significant independent predictor for the presence of sinonasal polyposis. This might be explained by the fact that rhinorrhea is the most objective symptom and therefore more easily recognized by parents than, for example, nasal obstruction. Our findings stress the importance of detailed history taking in children with CF and focusing on objective symptoms (e.g., mouth breathing instead of nasal obstruction).

Several authors have reported that patients with CF and nasal polyps have better pulmonary function and greater weight and height. Less frequently colonized by Staphylococcus aureus, more frequently colonized by Pseudomonas aeruginosa, and are more frequently male than children without nasal polyps. However, others could not confirm the correlation of these clinical characteristics with the presence of nasal polyps. In our total population, significant univariate predictors for the presence of sinonasal polyposis were male sex, good pulmonary function, and low CRP levels; in the symptomatic population, older age was also a significant predictor.

No medical treatment has proven effective in preventing progression of rhinologic complications in children with CF. Recently, the first randomized controlled trial of topical steroid treatment for nasal polyps in adult patients with CF has been performed, showing a statistically significant reduction in polyp size compared with placebo. However, no significant reduction in symptoms in the steroid-treated group could be demonstrated. Also, the

### Table 3. Independent Predictors of Sinonasal Polyposis in Symptomatic Population

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>Odds Ratio (95% CI)</th>
<th>Regression Coefficient</th>
<th>Contribution to Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>2.9 (1.1-7.5)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥10 y</td>
<td>2.6 (1.0-6.6)</td>
<td>0.9</td>
<td>1</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>2.7 (1.1-7.0)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>FVC ≥70% predicted</td>
<td>7.2 (1.8-29.1)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>ROC area</td>
<td>0.77</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval; ROC, receiver operating characteristic curve. Odds ratios and regression coefficients are adjusted for overoptimism by bootstrapping.

### Table 4. Number of Symptomatic Patients With and Without Sinonasal Polyposis Across Categories of Risk Score

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>Number of Subjects</th>
<th>Polyposis</th>
<th>No Polyposis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31</td>
<td>54</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>34</td>
<td>26</td>
</tr>
</tbody>
</table>

*Risk score was obtained from the following scoring rule: 1 (male sex) + 1 (age ≥10 years) + 1 (rhinorrhea) + 2 (forced vital capacity ≥70%).
†Number of subjects per score category.
therapeutic effectiveness of functional endoscopic sinus surgery has not been established in a randomized controlled trial, but various studies report a statistically significant reduction of symptoms after surgery.8,18

When evidence becomes available that medical and/or surgical treatment is effective in preventing progression of sinonasal polyposis in children with CF, there might be a good indication to involve the ORL physician routinely in the follow-up of these children. For now, our study showed that selection of “high-risk” patients for ORL referral on the basis of symptoms and clinical characteristics is of little value.

We demonstrated that in the children with ORL symptoms, using a scoring rule including the predictors male sex, age 10 years or older, symptoms of rhinorrhea, and FVC values 70% or greater of those predicted, the presence of sinonasal polyposis could be reasonably predicted (positive predictive value, 86%; negative predictive value, 71%). By using this simple scoring rule, referral to an ORL physician could become more effective. Although internal validation of the model by bootstrapping techniques demonstrated that the model is robust, the actual performance needs further external validation.

In conclusion, sinonasal polyps are present in half of the children with CF, but only 59% of those with polyps are symptomatic. As children with CF underreport their ORL symptoms, a detailed ORL history of each patient should be obtained regularly and should focus on objective symptoms. In an unselected population of children with CF, no combination of ORL symptoms and clinical characteristics could accurately predict the presence of sinonasal polyposis. In patients with CF and ORL symptoms, the presence of sinonasal polyposis could be reasonably predicted using a predictive model that includes male sex, age 10 years or older, symptoms of rhinorrhea, and FVC values 70% or greater of those predicted. A scoring rule including these independent predictors could reasonably classify children with CF and nasal symptoms into a category with increased risk for sinonasal polyposis, thus facilitating the decision on ORL referral.

Accepted for publication May 20, 2002.


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