Premiere Publications from The Triological Society

Read all three of our prestigious publications, each offering high-quality content to keep you informed with the latest developments in the field.

**The Laryngoscope**
Founded in 1896
Editor-in-Chief: Michael G. Stewart, MD, MPH
The leading source for information in head and neck disorders.
[Laryngoscope.com](http://Laryngoscope.com)

**Investigative Otolaryngology**
Editor-in-Chief: D. Bradley Welling, MD, PhD, FACS
Rapid dissemination of the science and practice of otolaryngology-head and neck surgery.
[InvestigativeOto.com](http://InvestigativeOto.com)

**ENTtoday**
A publication of the Triological Society
Editor-in-Chief: Alexander Chiu, MD
Must-have timely information that Otolaryngologist-head and neck surgeons can use in daily practice.
[Enttoday.org](http://Enttoday.org)

WILEY
Relationship Between Chronic Rhinosinusitis Exacerbation Frequency and Asthma Control

Raphael G. Banoub, BS; Katie M. Phillips, MD; Lloyd P. Hoehle, BS, BA; David S. Caradonna, MD, DMD; Stacey T. Gray, MD; Ahmad R. Sedaghat, MD, PhD

Objectives/Hypothesis: To determine the association between the frequency of acute chronic rhinosinusitis (CRS) exacerbations (AECRS) and the degree of asthma control in asthmatic CRS patients.

Study Design: Cross-sectional study.

Methods: We prospectively recruited 108 asthmatic CRS patients as participants. Asthma control was assessed using the Asthma Control Test (ACT). The frequency of AECRS was assessed using three previously described indirect metrics for AECRS: the frequency of patient-reported sinus infections, CRS-related antibiotics use, and CRS-related oral corticosteroids use in the last 3 months. CRS symptom severity was measured using the 22-item Sinonasal Outcome Test (SNOT-22). Associations between ACT score and metrics for AECRS were performed using linear regression while controlling for clinical and demographic characteristics, including SNOT-22 score.

Results: ACT score was significantly and negatively associated with the frequency of patient-reported sinus infections (adjusted linear regression coefficient $\beta = -1.2$, 95% confidence interval [CI]: $-2.3$ to $-0.1$, $P = .033$), CRS-related antibiotics courses (adjusted $\beta = -1.4$, 95% CI: $-2.3$ to $-0.5$, $P = .004$), and CRS-related oral corticosteroid courses (adjusted $\beta = -1.5$, 95% CI: $-2.5$ to $-0.5$, $P = .004$) in the last 3 months, independent of characteristics including SNOT-22 score. Poor asthma control could be detected using one or more sinus infections (70.6% sensitivity, 47.3% specificity), CRS-related antibiotics (50.0% sensitivity, 73.0% specificity), or CRS-related oral corticosteroids (58.8% sensitivity, 71.6% specificity) in the last 3 months.

Conclusions: AECRS are negatively associated with the level of asthma control in asthmatic CRS patients, independent of CRS symptom severity. These results highlight AECRS as a distinct clinical manifestation of CRS that should be routinely assessed in CRS patients.

Key Words: Chronic rhinosinusitis, acute exacerbations, asthma control, 22-item Sinonasal Outcome Test, antibiotics, oral corticosteroids.

Level of Evidence: 2c.

INTRODUCTION

Chronic rhinosinusitis (CRS) is an inflammatory disease of the paranasal sinus mucosa that causes a significant detriment to quality of life, results in billions of dollars in related costs, and has a largely unknown pathophysiology, although multiple possible mechanisms have been proposed. The natural history of CRS includes chronic nasal and extranasal symptoms as well as acute and transient increases in symptoms referred to as acute exacerbations of CRS (AECRS). One additional clinical manifestation of CRS is the exacerbation of comorbid pulmonary diseases, in particular asthma.

The relationship between CRS and asthma is not only an epidemiological one, characterized by common comorbidity of these diseases, but also based on clinical and pathophysiologic commonalities as well. Like CRS, asthma is an inflammatory disease of the airway (albeit lower airway), whose natural history includes pulmonary and extra-pulmonary symptoms overlain with acute asthma exacerbations. Moreover, many of the cellular and molecular inflammatory mediators of asthma have also been identified as playing an important role in CRS.

Given the many shared features of CRS and asthma, it is not surprising that these diseases can impact each other's disease course. This cross-disease interplay not only introduces unique challenges in the care of the asthmatic CRS patient, but also may provide future avenues for management (e.g., treatment of one disease through better control of the other). Previous work has shown that comorbid CRS is associated with poorer asthma outcomes.

From the Wayne State University School of Medicine (R.G.B.), Detroit, Michigan; Department of Otolaryngology (B.G.B., K.M.P., L.P.H., D.S.C., S.T.G., A.R.S.), Harvard Medical School, Boston, Massachusetts; Department of Otolaryngology (R.G.B., K.M.P., L.P.H., S.T.G., A.R.S.), Massachusetts Eye and Ear Infirmary, Boston, Massachusetts; Division of Otolaryngology (D.S.C., A.R.S.), Beth Israel Deaconess Medical Center, Boston, Massachusetts; and the Department of Otolaryngology and Communications Enhancement (A.R.S.), Boston Children’s Hospital, Boston, Massachusetts, U.S.A.

Editor’s Note: This Manuscript was accepted for publication August 14, 2017.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Send correspondence to Ahmad R. Sedaghat, MD, PhD, Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, MA 02114. E-mail: ahmad.sedaghat@mei.harvard.edu

DOI: 10.1002/lary.26901

Laryngoscope 128: May 2018
in general.\textsuperscript{16–18} The level of CRS symptom severity is negatively associated with the level of asthma control.\textsuperscript{11,12} Specifically, increasing CRS symptom severity is associated with poorer levels of asthma control. However, AECRS have been identified as clinical manifestations of CRS, whose impact on patients is distinct from the impact of chronic CRS symptomatology.\textsuperscript{10} It is therefore possible that the frequency of AECRS may be independently associated with decreased asthma control. In support of this possibility, previous work has also shown that asthma exacerbations are likely to follow AECRS in asthmatic patients.\textsuperscript{19} In this study, we hypothesized that frequency of AECRS reported by asthmatic CRS patients would be associated with poorer asthma control, so we sought to determine the relationship between AECRS frequency and asthma control levels in asthmatic CRS patients.

MATERIALS AND METHODS

Study Participants

This study was approved by the Massachusetts Eye and Ear Infirmary Human Studies Committee. Adult patients (age 18 years or older) with CRS were recruited prospectively and provided informed consent for inclusion into this study. All participants met consensus, guideline-established criteria for CRS.\textsuperscript{20} Exclusion criteria included comorbid diagnoses of 1) vasculitis, 2) cystic fibrosis, 3) sarcoidosis, and 4) immunodeficiency. To remove the confounding effect of recent endoscopic sinus surgery, patients who had endoscopic sinus surgery within the last 6 months were excluded.

Study Design and Data Collection

This study was designed as a cross-sectional study. All data were collected at enrollment. Demographic information including age, gender, and race were collected. Any patient who was an active smoker or reported a history of being a tobacco smoker in the past was a smoker for this study. At enrollment, participants were assessed by the evaluating physician for a history of asthma diagnosed based on consensus guidelines as well as a history of aeroallergen hypersensitivity based on formal allergy testing.\textsuperscript{13,21} Participants were interviewed to determine if they had a history of previous sinus surgery or a history of aspirin sensitivity. The presence of nasal polyps was determined based on nasal endoscopy, from which a Lund-Kennedy endoscopy score was also calculated.\textsuperscript{22} Intranasal corticosteroid (spray or irrigation) use as well as use of an inhaled corticosteroid were also assessed. AECRS were assessed using three previously described metrics, the number of patient-reported 1) sinus infections, 2) CRS-related antibiotic courses, and 3) CRS-related oral corticosteroid courses, each in the last 3 months.\textsuperscript{10,23} All participants also completed the validated 22-item Sinonasal Outcome Test (SNOT-22) survey,\textsuperscript{24} which provides a quantitative measure of CRS symptom severity. Finally, all participants completed an Asthma Control Test (ACT) to assess asthma control, and an ACT score less than 20 was deemed to be consistent with poor asthma control.\textsuperscript{25}

Statistical Analysis

All analysis was performed using the statistical software package R (The R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org).\textsuperscript{26} A total of 108 participants were recruited to have 80% power to detect an association of medium effect size (Cohen’s $d = 0.15$) between ACT score (as dependent variable) and each of the three metrics for AECRS previously described at a significance of 0.05 and while controlling for 10 other covariates. Associations with the ACT score as the dependent variable were determined with univariate and multivariable linear regression. Associations with poor asthma control (i.e., having an ACT score less than 20) were determined with univariate and multivariable logistic regression. Multivariable models between asthma control and our metrics for AECRS controlled for age, gender, smoking history, aeroallergen hypersensitivity, intranasal corticosteroid use, inhaled corticosteroid use, polyps, history of previous sinus surgery, endoscopy score, and SNOT-22 score. To identify and characterize the sensitivity and specificity of using our metrics for AECRS frequency for the detection of poorly controlled asthma in our participants, we analyzed receiver operating characteristic (ROC) curves with the pROC package.\textsuperscript{27} The area under the ROC curve (AUC) was calculated with the trapezoid rule using the auc() function, and the 95% confidence interval of the AUC was calculated by performing 2,000 bootstraps of the data with the ci() function. The $P$ value for significance of the ROC curve was determined by Wilcoxon rank sum test.

RESULTS

Characteristics of Study Participants

We recruited a total of 108 asthmatic participants with CRS, with mean age of 49.4 (standard deviation [SD]: 15.3) years, consisting of 39.8% males and 60.2% females, and their demographic and clinical characteristics are summarized in Table I. Of note, 69.9% of participants had nasal polyps and 54.6% had a history of prior endoscopic sinus surgery. The mean SNOT-22 score was 44.5 (SD = 24.2) and the mean endoscopy score was 4.8 (SD = 3.1). In examining our patient-reported metrics for AECRS in the past 3 months, the mean number of sinus infections was 0.8 (SD = 0.9), the mean number of CRS-related antibiotics courses taken was 0.6 (SD = 1.0), and the mean number of CRS-related oral corticosteroids courses was also 0.6 (SD = 1.0). With respect to asthma characteristics, 54.6% of participants reported using an inhaled corticosteroid, and the mean ACT score was 20.2 (SD = 5.0), with 31.5% percent having poorly controlled asthma (ACT score less than 20).

Asthma Control Is Associated With Frequency of AECRS

We next sought to determine if the ACT score was associated with our metrics of AECRS frequency (Fig. 1 and Table II). We found that the ACT score was negatively associated the number of patient-reported sinus infections (linear regression coefficient [$\beta$] = −2.1, 95% confidence interval [CI]: −3.1 to −1.0, $P < .001$), CRS-related antibiotics courses ($\beta = −1.2$, 95% CI: −2.1 to −0.2, $P = .016$), and CRS-related oral corticosteroids courses ($\beta = −1.6$, 95% CI: −2.6 to −0.7, $P = .001$) in the last 3 months on univariate association. Using our multivariable regression models, which controlled for clinical and demographic characteristics including SNOT-22 score and endoscopy score, these associations between ACT score and patient-reported sinus infections ($\beta = −1.2$, 95% CI: −2.3 to −0.1, $P = .033$), CRS-related antibiotics courses ($\beta = −1.4$, 95% CI: −2.3 to −0.5, $P = .001$)}
and CRS-related oral corticosteroid courses ($\beta = -1.5$, 95% CI: $-2.5$ to $-0.5$, $P = .004$) in the last 3 months remained statistically significant. Thus, our metrics for AECRS frequency were independently associated with asthma control level.

### Metrics for CRS Severity—Including Symptom Severity and AECRS Frequency—May Be Used to Detect Poorly Controlled Asthma

We next sought to determine whether any metrics of CRS severity could be used to detect asthmatic CRS patients with poorly controlled asthma (ACT score less than 20). We generated ROC curves to detect the accuracy of our metrics for AECRS, SNOT-22, and endoscopy score in detecting patients with poor asthma control (Fig. 2). The AUC of the ROC curves was calculated to determine if any of these measures of CRS severity would detect poor asthma control in our participants better than a random test in a statistically significant manner (AUC greater than 0.5). Although endoscopy score was not found to be a useful test for detecting poor asthma control, (AUC = 0.552, 95% CI: 0.431 to 0.673, $P = .388$), patient-reported sinus infections (AUC = 0.625, 95% CI: 0.517 to 0.732, $P = .023$), patient-reported CRS-related antibiotics usage (AUC = 0.615, 95% CI: 0.513 to 0.717, $P = .024$), patient-reported CRS-related oral corticosteroid usage (AUC = 0.648, 95% CI: 0.546 to 0.750, $P = .005$), and SNOT-22 (AUC = 0.733, 95% CI: 0.636 to 0.830, $P < .001$) all had ROC curve AUCs that were significantly greater than 0.5. Optimal cutoffs for these metrics—maximizing the sum of sensitivity and specificity—are summarized in Table III. Although a SNOT-22 score greater than or equal to 45 provides the best sensitivity at 82.4% (with 67.6% specificity) for detecting poor asthma control, using a criteria of at least one patient-reported course of either CRS-related antibiotics or oral corticosteroids in the last three months provides the best specificity at over 70% for detecting poor asthma control. In combining these tests, having either SNOT-22 greater than 45 or having taken both one or more CRS-related antibiotics and one or more CRS-related oral corticosteroids in the last 3 months provided 88.2% sensitivity with 62.2% specificity in detecting asthmatic CRS patients with poor asthma control.

### TABLE I. Characteristics of Study Participants.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study Participants, N = 108</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>Age, yr (SD)</td>
<td>49.4 (15.3)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>39.8%</td>
</tr>
<tr>
<td>Female</td>
<td>60.2%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>62.0%</td>
</tr>
<tr>
<td>Black or African American</td>
<td>2.8%</td>
</tr>
<tr>
<td>Other</td>
<td>4.6%</td>
</tr>
<tr>
<td>Declined to respond</td>
<td>30.6%</td>
</tr>
<tr>
<td>Smoking</td>
<td>39.8%</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>Aspirin sensitivity</td>
<td>14.8%</td>
</tr>
<tr>
<td>Aeroallergen hypersensitivity</td>
<td>68.5%</td>
</tr>
<tr>
<td>Asthma characteristics</td>
<td></td>
</tr>
<tr>
<td>Inhaled corticosteroid controller use</td>
<td>54.6%</td>
</tr>
<tr>
<td>ACT score, mean (SD)</td>
<td>20.2 (5.0)</td>
</tr>
<tr>
<td>CRS characteristics</td>
<td></td>
</tr>
<tr>
<td>Nasal polyps</td>
<td>69.4%</td>
</tr>
<tr>
<td>Previous sinus surgery</td>
<td>54.6%</td>
</tr>
<tr>
<td>Intranasal steroid use</td>
<td>79.6%</td>
</tr>
<tr>
<td>Endoscopy score, mean (SD)</td>
<td>4.8 (3.1)</td>
</tr>
<tr>
<td>SNOT-22 score, mean (SD)</td>
<td>44.5 (24.2)</td>
</tr>
<tr>
<td>Sinus infections in the last 3 months, mean (SD)</td>
<td>0.8 (0.9)</td>
</tr>
<tr>
<td>CRS-related antibiotic courses in the last 3 months, mean (SD)</td>
<td>0.6 (1.0)</td>
</tr>
<tr>
<td>CRS-related oral corticosteroid courses in the last 3 months, mean (SD)</td>
<td>0.6 (1.0)</td>
</tr>
</tbody>
</table>

ACT = Asthma Control Test; CRS = chronic rhinosinusitis; SD = standard deviation; SNOT-22 = 22 item Sinonasal Outcome Test.

Fig. 1. Scatter plot of ACT score versus patient reported number of (A) sinus infections, (B) CRS-related antibiotics courses, and (C) CRS-related oral corticosteroids courses, all in the last 3 months. ACT = Asthma Control Test; CRS = chronic rhinosinusitis.

Laryngoscope 128: May 2018

Banoub et al.: CRS Exacerbation and Poor Asthma Control
DISCUSSION

CRS has a notable relationship with and negative impact on asthma control. Poor asthma control has been previously been associated with decreased quality of life, reduced participation in recreational activities, and lost workplace productivity. Poor asthma control is also predictive of future asthma exacerbations, as well as asthma-related emergency department visits and hospitalizations. Because acute exacerbations are a distinct clinical manifestation of CRS, we investigated the relationship between AECRS frequency and the level of asthma control in asthmatic CRS patients. We found that the frequency of AECRS was significantly and negatively associated with the level of asthma control consistently across all of our metrics for AECRS frequency, and in all cases this association was independent of CRS symptom severity. Additionally, our metrics for frequency of AECRS—in particular patient-reported number of CRS-related antibiotics courses or oral corticosteroids courses in the past 3 months—in combination with SNOT-22 score criteria, could be used to predict poor asthma control in asthmatic CRS patients with 88.2% sensitivity and 62.2% specificity. These results not only provide further evidence for the intertwined nature of the CRS and asthma disease processes, but also provide further evidence for AECRS as a distinct clinical manifestation of CRS that impacts patients independent of the CRS symptoms severity.

Our findings are supportive of the unified airway and the interdependence between both health and disease in the upper and lower respiratory tracts. This relationship has been historically typified by the strong

![Fig. 2. ROC curve to detect poorly controlled asthma (ACT score < 20) using independent variables of patient-reported number of (A) sinus infections, (B) CRS-related antibiotics courses, and (C) CRS-related oral corticosteroids courses, each in the last 3 months, as well as (D) SNOT-22 score and (E) endoscopy score. The points reflecting the cutoff for each statistically significant independent variable (1 for A, B, C; 45 for D), which are summarized in Table III and maximized the sum of sensitivity and specificity, are marked in each panel. ACT = Asthma Control Test; CRS = chronic rhinosinusitis; ROC = receiver operating characteristic; SNOT-22 = 22-item Sinonasal Outcome Test. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]](image-url)
Our results should be interpreted in the context of the limitations of our study. Our three measures of AECRS rely on patient recall, which may lead to recall bias. Because the symptoms of CRS and asthma may overlap (for example, cough), it is also possible that the patient-reported CRS-related oral corticosteroids used may have been prescribed for CRS and/or asthma. Additionally, our study identified a cross-sectional association between AECRS frequency and asthma control level. Nevertheless, the science behind what is likely to be shared inflammatory pathophysiology between the upper and lower respiratory tracts is complex, and we must therefore acknowledge that there may be additional variables not accounted for that could be confounding our participants’ coexisting asthma and CRS. Additionally, although our study reports the incremental decrease in asthma control level associated with AECRS frequency, our study is not an interventional study and does not show how therapeutically decreasing the frequency of CRS exacerbations would impact the level of asthma control. Nevertheless, we believe that the results of this study pave the way for future studies to explore how specific reductions in AECRS frequency may improve the level of asthma control in asthmatic CRS patients.

CONCLUSION

The frequency of AECRS is associated with poorer asthma control in asthmatic CRS patients independent of CRS symptom severity. Moreover, metrics for the frequency of AECRS—the number of patient-reported sinus infections, CRS-related antibiotics courses, and CRS-related oral corticosteroid courses each in the last 3 months—in combination with the SNOT-22 score may be used as one means to trigger evaluation for poor asthma control in asthmatic CRS patients. The results of our study highlight AECRS as a distinct clinical manifestation of CRS that should be assessed in the clinical setting and used to prompt further assessment of poor asthma control in asthmatic CRS patients.

BIBLIOGRAPHY

5. London NR, Lane AP. Innate immunity and chronic rhinosinusitis: what we have learned from animal models. Laryngoscope Investig Otolaryngol 2016;1:49–56.