Clinical Traits Characterizing an Exacerbation-Prone Phenotype in Chronic Rhinosinusitis

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Abstract

Objective. Acute exacerbation of chronic rhinosinusitis (AECRS) is associated with significant quality-of-life decreases. We sought to determine characteristics associated with an exacerbation-prone phenotype in chronic rhinosinusitis (CRS).

Study Design. Cross-sectional.

Setting. Tertiary care rhinology clinic.

Subjects. Patients with CRS (N = 209).

Methods. Patient-reported number of sinus infections, CRS-related antibiotics, and CRS-related oral corticosteroids taken in the last 12 months were used as metrics for AECRS frequency. Sinonasal symptom burden was assessed with the 22-item Sinonasal Outcome Test (SNOT-22). Ninety patients reporting 0 for all AECRS metrics were considered to have had no AECRS in the prior 12 months. A total of 119 patients reported ≥3 on at least 1 AECRS metric and were considered as having an exacerbation-prone phenotype. Characteristics associated with patients with an exacerbation-prone phenotype were identified with exploratory regression analysis.

Results. An exacerbation-prone phenotype was positively associated with comorbid asthma (adjusted odds ratio [ORadj] = 3.68, 95% CI: 1.42-9.50, P = .007) and SNOT-22 (ORadj = 1.06, 95% CI: 1.04-1.09, P < .001). Polyps were negatively associated (ORadj = 0.27, 95% CI: 0.11-0.68, P = .005) with an exacerbation-prone phenotype. SNOT-22 score ≥24 identified patients with an exacerbation-prone phenotype with a sensitivity of 93.3% and a specificity of 57.8%. Having either a SNOT-22 score ≥24 with a nasal subdomain score ≥12 or a SNOT-22 score ≥24 with an ear/facial discomfort subdomain score ≥3 provided >80% sensitivity and specificity for detecting patients prone to exacerbation.

Conclusions. In total, these results point to a CRS exacerbation-prone phenotype characterized by high sinonasal disease burden with comorbid asthma but interestingly without polyps.

Keywords
chronic rhinosinusitis, exacerbations, asthma, nasal polyps, antibiotics

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Chronic rhinosinusitis (CRS) is an inflammatory disease characterized by the presence of cardinal sinonasal symptoms lasting ≥12 weeks with evidence of inflammation on imaging or endoscopic examination, as defined by consensus diagnostic guideline criteria.1 Clinically, CRS is commonly classified into 2 phenotypes—CRS with nasal polyps and CRS without nasal polyps2—although this broad classification often fails to capture the heterogeneity of the disease process and the spectrum of clinical presentations. Therefore, much work has been done to further characterize CRS to better understand the varied underlying pathophysiologies that lead to different phenotypes, natural history of the disease processes, and therapeutic options.3

Adding to the complexity of the disease, patients with CRS can also have flares of their symptoms, leading to acute exacerbation of CRS (AECRS). AECRS is defined as acute worsening of symptoms with return to baseline, often

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requiring a transient escalation in treatment, such as a
course of oral antibiotics or corticosteroids. AECRS can
affect patients with CRS in a variety of ways, including
increased risk of orbital or intracranial complications,3
decreased quality of life (QOL),5 decreased productivity,6
and potential for exacerbation of comorbid disease, such as
asthma,7,8 which may lead to further QOL and productivity
detrimen.6,9 Prior studies of AECRS have investigated the
immunologic profile,10 bacterial etiology,9,11 and treatment12
of AECRS. However, little is still known about risk factors
for development of AECRS and which patients may be most
susceptible to suffering the consequences of AECRS.

Motivated by research on asthma, where an exacerbation-
prone phenotype of patients with asthma has been extensively
studied and characterized,13 it has been proposed that there is
a phenotype of CRS characterized by frequent AECRS.14
However, a full characterization of the exacerbation-prone
CRS phenotype is still lacking. A better understanding of the
exacerbation-prone CRS phenotype would help to elucidate
the driving pathophysiology in these patients, which could
also lead to improved treatment—and therefore QOL and
health care costs—in this patient population. In this study, we
sought to determine characteristics associated with an
exacerbation-prone phenotype of CRS to better describe and
identify patients of this phenotype.

Methods

Study Participants

This study was approved by the Massachusetts Eye and Ear
Infirmary Human Studies Committee. Adult patients, aged
18 years or older, meeting consensus guideline criteria for
CRS1 were prospectively recruited between October 2017
and June 2018. Only patients reporting either 0 or >3
AECRSs in the prior year were included. All study partici-
pants provided informed consent for inclusion. Exclusion
criteria included comorbid diagnoses of vasculitis, cystic
fibrosis, sarcoidosis, and immunodeficiency as well as endo-
scopic sinus surgery within the past 6 months (to remove
the confounding effects of recent sinus surgery).

Study Design and Data Collection

This study was a cross-sectional study of patients with CRS.
Demographic and relevant medical comorbidities were col-
lected at the time of enrollment. Any patient who was an
active smoker or reported a history of being a tobacco
smoker was considered a smoker for this study.15,16 Patients
were directly asked about, and their charts reviewed for,
an established diagnosis of migraine or other headache disor-
der. CRS symptom severity was assessed with the 22-item
Sinonasal Outcome Test (SNOT-22).17 The validated nasal,
sleep, ear/facial discomfort, and emotional subdomains of
the SNOT-22 were calculated as previously described.18,19
At enrollment, patients were asked to report the number of
sinus infections, courses of CRS-related antibiotics, and
courses of CRS-related oral corticosteroids that they had
over the preceding 12 months.20

The number of sinus infections, courses of CRS-related
antibiotics, and courses of CRS-related oral corticosteroids
over the prior 12 months were taken as metrics for AECRS
frequency.20,21 Patients who reported >3 of any AECRS metric (each corresponding to a different time point) in the
past 12 months were considered to have an exacerbation-
prone phenotype. We chose this criterion due to past work
showing that 1 AECRS per 3 months (>3 over a 12-month
period) was considered to be uncontrolled CRS based on
AECRS criteria.4,21 To identify characteristics associated
with this phenotype, these participants with high-frequency
AECRS were compared with participants reporting zero of
our AECRS metrics in the preceding 12 months.

Statistical Analysis

All analysis was performed with the statistical software
package R (www.r-project.org). Standard descriptive statis-
tics were performed. Univariate and multivariable logistic
regression were used to examine the association between
the exacerbation-prone phenotype (vs reporting no AECRS
in the preceding 12 months) as the dependent variable and
patients’ clinical characteristics as the independent vari-
ables. An exploratory multivariable logistical regression
analysis was performed with covariates of participant age,
sex, smoking history, aeroallergen hypersensitivity, comor-
bid asthma, nasal polyps, history of previous endoscopic
sinus surgery, use of intranasal corticosteroids, and SNOT-
22 score. In the multivariable analysis, significant predictors
were identified via backward elimination, with a P value
cutoff of .100. The final multivariable results were cross-
validated by bootstrapping the data >100 iterations. For
each variable retained in the final model, a P value and a
log odds ratio (OR) were calculated. A P value <.05 was
deeded to be statistically significant.

Receiver operating characteristic (ROC) analysis was
performed with the pROC package. The area under the
ROC curve was calculated with the trapezoid rule and the
auc() function. The 95% CI of the area under the curve was
calculated by performing 2000 bootstraps of the data with
the ci() function. The P value for significance of the ROC
curve was determined by the Wilcoxon rank sum test.

Results

Characteristics of Study Participants

A total of 209 participants with CRS were included: 90
without any AECRS and 119 reporting >3 occurrences of
any AECRS metric in the prior 12 months. In the no-
AECRS group, the mean age was 55.3 years (SD, 16.5); 21.1% had comorbid asthma; 11.1% had a prior diagnosis
of migraine or other headache disorder; 43.3% had nasal
polyps; and 35.6% had a history of sinus surgery. In the
exacerbation-prone group, the mean age was 48.6 years
(SD, 16.6); 39.5% had comorbid asthma; 18.5% had a prior
diagnosis of migraine or other headache disorder; 25.3%
had nasal polyps; and 54.6% had a history of sinus surgery.
The remainder of their clinical and demographic characteris-
tics are shown in Table 1.
Table 1. Characteristics of Study Participants (N = 209).

<table>
<thead>
<tr>
<th></th>
<th>Participants, Mean (SD) or %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No AECRS</td>
</tr>
<tr>
<td></td>
<td>Exacerbation Prone</td>
</tr>
<tr>
<td></td>
<td>(n = 90)</td>
</tr>
<tr>
<td>(n = 119)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>55.3 (16.5)</td>
</tr>
<tr>
<td></td>
<td>48.6 (16.6)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>60.0</td>
</tr>
<tr>
<td>Female</td>
<td>40.0</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
</tr>
<tr>
<td>Aerocallergen hypersensitivity</td>
<td>38.9</td>
</tr>
<tr>
<td>Asthma</td>
<td>21.1</td>
</tr>
<tr>
<td>Aspirin sensitivity</td>
<td>4.4</td>
</tr>
<tr>
<td>Migraine or other headache disorder</td>
<td>11.1</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CRS characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Nasal polyps</td>
<td>43.3</td>
</tr>
<tr>
<td>Previous sinus surgery</td>
<td>35.6</td>
</tr>
<tr>
<td>Intranasal steroid use</td>
<td>32.2</td>
</tr>
<tr>
<td>SNOT-22 score</td>
<td>25.1 (18.7)</td>
</tr>
<tr>
<td>In the last 12 mo</td>
<td>49.2 (19.0)</td>
</tr>
<tr>
<td>Sinus infections</td>
<td>0 (0)</td>
</tr>
<tr>
<td>CRS-related antibiotic courses</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Corticosteroid courses</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

**Abbreviations:** AECRS, acute exacerbation of chronic rhinosinusitis; CRS, chronic rhinosinusitis; SNOT-22, 22-item Sinonasal Outcome Test.

**Associations with Exacerbation-Prone CRS Phenotype**

We first checked for characteristics associated with the exacerbation-prone phenotype (Table 2). On univariate analysis, the exacerbation-prone phenotype was positively associated with comorbid asthma (OR = 2.44, 95% CI: 1.30-4.56, P = .005) and SNOT-22 score (adjusted OR [ORadj] = 1.07, 95% CI: 1.05-1.09, P < 0.001). The exacerbation-prone phenotype was negatively associated with nasal polyps (OR = 0.44, 95% CI: 0.24-0.79, P = .006). These associations remained statistically significant on multivariable analysis. The exacerbation-prone phenotype was positively associated with comorbid asthma (ORadj = 3.68, 95% CI: 1.42-9.50, P = .007) and SNOT-22 score (ORadj = 1.06, 95% CI: 1.04-1.09, P < .001) with a point estimate suggestive of an association with a history of sinus surgery (OR = 1.87, 95% CI: 0.91-3.83, P = .086). Polyps were negatively associated (ORadj = 0.27, 95% CI: 0.11-0.68, P = .005) with this phenotype.

**Associations of Exacerbation-Prone Phenotype with the SNOT-22 Subdomain Scores**

To gain further insight into the underlying reasons for the association of SNOT-22 score with the exacerbation-prone phenotype, we checked for associations between the exacerbation-prone phenotype and individual SNOT-22 subdomain scores. On univariate association, we found that all 4 subdomains were associated with the exacerbation-prone phenotype: nasal (OR = 1.14, 95% CI: 1.09-1.19, P < .001), sleep (OR = 1.09, 95% CI: 1.06-1.12, P < .001), ear/facial discomfort (OR = 1.25, 95% CI: 1.16-1.34, P < .001), and emotional (OR = 1.28, 95% CI: 1.10-1.49, P = .001). Using a multivariable regression model incorporating all 4 subdomain scores with the previous described covariates, we found that the nasal (OR = 1.12, 95% CI: 1.06-1.19, P < .001) and ear/facial discomfort (OR: 1.16, 95% CI: 1.05-1.29, P = .005) subdomain scores remained associated with the exacerbation-prone phenotype but not the sleep (OR = 1.02, 95% CI: 0.97-1.08, P = .339) and emotional (OR = 0.88, 95% CI: 0.67-1.16, P = .378) subdomain scores.

**CRS Exacerbation-Prone Phenotype Characterized by High Sinonasal Disease Burden with Comorbid Asthma but without Nasal Polyps**

Next, the accuracy of the predictors of the exacerbation-prone phenotype was evaluated. We used ROC analysis to identify threshold values of the SNOT-22 score or its subdomain scores to identify patients who were exacerbation prone (Table 3). SNOT-22 score and its nasal subdomain score were the 2 most accurate (based on area under the curve and the sum of sensitivity and specificity) for detecting patients who were exacerbation prone. A SNOT-22 score ≥24 provided a sensitivity of 93.3% and a specificity of 57.8% while, individually, a SNOT-22 nasal subdomain score ≥17 (out of 40) provided 74.8% sensitivity and 73.3% specificity for detecting patients who were exacerbation prone. In comparison, comorbid asthma had 39.5% sensitivity but 78.9% specificity, while not having polyps had 74.8% sensitivity but 44.4% specificity for identifying patients with the exacerbation-prone phenotype.

Combining patient symptom (ie, SNOT-22 score) characteristics led to accurate means of detecting patients who were exacerbation prone. A SNOT-22 score ≥24 with a nasal subdomain score ≥12 provided 82.3% sensitivity and 81.3% specificity for detecting patients with CRS who were exacerbation prone. Alternatively, a SNOT-22 score ≥24 with an ear/facial subdomain score ≥3 provided 84.7% sensitivity and 80.8% specificity for detecting patients with CRS who were exacerbation prone. Both these criteria had significant overlap, as 131 patients (of whom 102 were exacerbation prone) had a SNOT-22 score ≥24 with a nasal subdomain score ≥12, while 133 patients (of whom 102 were exacerbation prone) had a SNOT-22 score ≥24 with an ear/facial subdomain score ≥3. Ninety-three patients who were exacerbation prone met both these criteria (nasal subdomain score ≥12 and ear/facial discomfort score ≥3, with SNOT-22 score ≥24). Of the 9 patients who were exacerbation prone and who had a SNOT-22 score ≥24 and an ear/facial discomfort subdomain score ≥3 but a nasal subdomain score <12, only 1 had a known diagnosis of migraine or other headache disorder.
An AECRS is likely a multifactorial process involving the interplay between the immune system and allergens, bacteria, fungi, viruses, environmental toxins, or some other unknown immunostimulatory agent that triggers an inflammatory cascade resulting in an acute exacerbation of sinusonal inflammation and therefore sinonasal symptoms. Progress has been made to understand the local and systemic inflammatory response during an acute exacerbation\textsuperscript{10} and investigate specific bacterial etiologies,\textsuperscript{22} but the specifics underlying the pathophysiology and the natural history of AECRS have yet to be fully elucidated. More recently, it was shown that AECRS can be a major driver of morbidity, have significant QOL detriments, and increase the healthcare costs for patients who experience these exacerbations.\textsuperscript{5,6} In patients with CRS who have recurrent exacerbations, the downstream consequences—decreased QOL and lost productivity—can rapidly compound upon one another. Unfortunately, the ability to identify these patients who may be exacerbation prone, by understanding their characteristics and risk factors, is nascent such that they can be more appropriately treated and more focused research can be performed. In this study, we focused on patients with CRS who had $>3$ AECRS episodes in the preceding year, and we compared them with patients with CRS who had no AECRS in the preceding year. We found that a SNOT-22 score $\geq 24$, the lack of nasal polyps, and comorbid asthma characterize patients with highly recurrent AECRS. Related to the SNOT-22 score, the burden of nasal symptoms and the burden of ear/facial discomfort symptoms were most predictive of being exacerbation prone. These same characteristics could also be used to accurately identify patients with high AECRS reoccurrence or what we identified as an exacerbation-prone phenotype.

The model of the exacerbation-prone phenotype has been more extensively studied in asthma. The clinical characteristics of this asthma phenotype include traits such as a history of smoking, psychosocial factors, medication nonadherence, comorbid CRS, and history of nonsteroidal anti-inflammatory medication intolerance. Additionally, intrinsic host factors, such as deficient epithelial cell production of antiviral type I interferons, have also been found to possibly lead to an exacerbation-prone phenotype. These same characteristics could also be used to accurately identify patients with high AECRS reoccurrence or what we identified as an exacerbation-prone phenotype.

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### Table 2. Characteristics Associated with Exacerbation-Prone Phenotype of CRS.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariate Analysis</th>
<th>Multivariable Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>$P$ Value</td>
</tr>
<tr>
<td>Age</td>
<td>0.98 (0.96-0.99)</td>
<td>.005</td>
</tr>
<tr>
<td>Sex</td>
<td>2.96 (1.68-5.23)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.81 (0.46-1.43)</td>
<td>.465</td>
</tr>
<tr>
<td>Aeroallergen hypersensitivity</td>
<td>1.88 (1.07-3.29)</td>
<td>.035</td>
</tr>
<tr>
<td>Asthma</td>
<td>2.44 (1.30-4.56)</td>
<td>.005</td>
</tr>
<tr>
<td>Nasal polyps</td>
<td>0.44 (0.24-0.79)</td>
<td>.006</td>
</tr>
<tr>
<td>Migraine or other headache disorder</td>
<td>1.81 (0.81-4.05)</td>
<td>.146</td>
</tr>
<tr>
<td>Intranasal corticosteroids use</td>
<td>1.69 (0.95-2.99)</td>
<td>.072</td>
</tr>
<tr>
<td>Previous endoscopic sinus surgery</td>
<td>1.96 (1.11-3.46)</td>
<td>.021</td>
</tr>
<tr>
<td>SNOT-22 score</td>
<td>1.07 (1.05-1.09)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: CRS, chronic rhinosinusitis; SNOT-22, 22-item Sinonasal Outcome Test.

### Table 3. Accuracy of the SNOT-22 Score and Associated Subdomains to Detect Patients with CRS Who Are Exacerbation Prone.$^a$

<table>
<thead>
<tr>
<th>SNOT-22</th>
<th>Optimal Cutoff Value</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>AUC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 24$</td>
<td>93.3</td>
<td>57.8</td>
<td>0.824 (0.765-0.882)</td>
<td></td>
</tr>
<tr>
<td>Subdomain scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal</td>
<td>$\geq 17$</td>
<td>74.8</td>
<td>73.3</td>
<td>0.790 (0.727-0.854)</td>
</tr>
<tr>
<td>Sleep</td>
<td>$\geq 7$</td>
<td>85.7</td>
<td>54.4</td>
<td>0.765 (0.700-0.830)</td>
</tr>
<tr>
<td>Ear/facial discomfort</td>
<td>$\geq 3$</td>
<td>90.8</td>
<td>55.6</td>
<td>0.786 (0.723-0.849)</td>
</tr>
<tr>
<td>Emotional</td>
<td>$\geq 1$</td>
<td>58.0</td>
<td>68.9</td>
<td>0.645 (0.577-0.713)</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the curve; CRS, chronic rhinosinusitis; SNOT-22, 22-item Sinonasal Outcome Test.

$^a$For each row, $P < .001$.

$^b$Maximizes the sum of sensitivity and specificity.

### Discussion

An AECRS is likely a multifactorial process involving the interplay between the immune system and allergens, bacteria, fungi, viruses, environmental toxins, or some other unknown immunostimulatory agent that triggers an inflammatory cascade resulting in an acute exacerbation of sinusonal inflammation and therefore sinonasal symptoms. Progress has been made to understand the local and systemic inflammatory response during an acute exacerbation\textsuperscript{10} and investigate specific bacterial etiologies,\textsuperscript{22} but the specifics underlying the pathophysiology and the natural history of AECRS have yet to be fully elucidated. More recently, it was shown that AECRS can be a major driver of morbidity, have significant QOL detriments, and increase the health care costs for patients who experience these exacerbations.\textsuperscript{5,6} In patients with CRS who have recurrent exacerbations, the downstream consequences—decreased QOL and lost productivity—can rapidly compound upon one another. Unfortunately, the ability to identify these patients who may be exacerbation prone, by understanding their characteristics and risk factors, is nascent such that they can be more appropriately treated and more focused research can be performed. In this study, we focused on patients with CRS who had $>3$ AECRS episodes in the preceding year, and we compared them with patients with CRS who had no AECRS in the preceding year. We found that a SNOT-22 score $\geq 24$, the lack of nasal polyps, and comorbid asthma characterize patients with highly recurrent AECRS. Related to the SNOT-22 score, the burden of nasal symptoms and the burden of ear/facial discomfort symptoms were most predictive of being exacerbation prone. These same characteristics could also be used to accurately identify patients with high AECRS reoccurrence or what we identified as an exacerbation-prone phenotype.

The model of the exacerbation-prone phenotype has been more extensively studied in asthma. The clinical characteristics of this asthma phenotype include traits such as a history of smoking, psychosocial factors, medication nonadherence, comorbid CRS, and history of nonsteroidal anti-inflammatory medication intolerance. Additionally, intrinsic host factors, such as deficient epithelial cell production of antiviral type I interferons, have also been found to possibly lead to an exacerbation-prone phenotype. These same characteristics could also be used to accurately identify patients with high AECRS reoccurrence or what we identified as an exacerbation-prone phenotype.

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associated with recurrent exacerbations.\textsuperscript{23} Further study of this phenotype in CRS would ideally lead to similar addressable targets.

Previous work has provided some preliminary insights for characterizing an exacerbation-prone phenotype in CRS. A recent large epidemiologic study followed the natural history of acute exacerbations of nasal and sinus symptoms in a general population of patients with and without CRS.\textsuperscript{24} The authors found that risk factors for acute exacerbations of nasal and sinus symptoms included CRS diagnosis, increased body mass index, asthma symptoms, hay fever, migraine symptoms, and history of sinus surgery. While this study of general nasal or sinus exacerbations provides insights into potential risk factors for AECRS, no conclusions could be drawn regarding specific risk factors for recurrent exacerbations in the patient population with CRS.\textsuperscript{24}

To further investigate characteristics of patients with CRS with recurrent exacerbations, our study compared 2 groups of patients with CRS—those without an AECRS in the past 12 months and those with >3 AECRS events in the past 12 months—which we considered to be reflective of an exacerbation-prone phenotype. We found that in patients with a high AECRS frequency, there was a positive association with comorbid asthma and SNOT-22 score, reflecting high sinonasal symptom burden. A positive association with a history of sinus surgery was also suggested. These findings are similar to risk factors previously described for general nasal and sinus exacerbations.\textsuperscript{24} Our findings suggest the possibility that patients with CRS with comorbid asthma and high sinonasal symptom burden may also have an increased likelihood of an underlying proinflammatory state conducive to recurrent AECRS and perhaps have an exacerbation-prone phenotype. More detailed study of the different symptoms reflected by the SNOT-22 also showed that the burden of nasal symptoms and symptoms related to ear/facial discomfort were most predictive of being exacerbation prone. While the association with the burden of nasal symptomatology is consistent with generally more severe sinus disease, the association of ear/facial discomfort symptoms with being exacerbation prone may suggest cephalalgia as a factor that influences the perception of AECRS. Although we diagnosed all of the included patients with CRS, we did not necessarily administer or confirm patient-reported AECRS metrics, such as past antibiotics use, which may call into question whether patients who report AECRS metrics were truly experiencing AECRS or some other phenomenon. However, the significant overlap of patients meeting both nasal symptom and ear/facial discomfort symptom criteria—as well as the lack of association between established diagnoses of migraine or other headache disorders and being exacerbation prone—seems to point more toward patients whose disease may be a greater driver of cephalalgia in general.

Interestingly, we additionally found a negative association between an exacerbation-prone phenotype and the presence of nasal polyps. These findings are similar to a previous study that found that patients with CRS with nasal polyps are less likely to use antibiotics, which could serve as a proxy for an exacerbation, relative to other patients with CRS.\textsuperscript{25} These findings could suggest that the underlying inflammatory pathways for CRS with nasal polyps may be distinct from the underlying etiologies for highly recurrent AECRS. In comparison to these finding, previous studies have identified inflammatory mediator profiles in the nasal secretions of patients with AECRS.\textsuperscript{10,26} However, these studies did not differentiate between patients with isolated or recurrent (ie, high frequency) AECRS. Our results do not conflict with the occurrence of AECRS in patients with nasal polyps, which these studies showed and characterized. However, the underlying pathophysiology in patients with CRS experiencing high-frequency AECRS may very well consist of a distinct inflammatory profile.

By identifying characteristics associated with an exacerbation-prone phenotype, we may be able to use these characteristics to identify those patients. Individually, a SNOT-22 score $\geq 24$, a SNOT-22 nasal subdomain score $\geq 17$, a SNOT-22 ear/facial discomfort subdomain score $\geq 3$, comorbid asthma, or the lack of nasal polyps provides either sensitive or specific means of identifying patients with this phenotype. By taking multiple characteristics into account, we found that having either a SNOT-22 score $\geq 24$ with a nasal subdomain score $\geq 12$ or a SNOT-22 score $\geq 24$ with an ear/facial discomfort subdomain score $\geq 3$ provided $>80\%$ sensitivity and specificity for detecting patients with an exacerbation-prone phenotype. Further characterization of which clinical characteristics are associated with AECRS can help to better predict which patients may have recurrent exacerbations and how to better treat, counsel, and study these patients.

This study should be interpreted in the context of limitations. AECRS is not well defined in the literature. Although patient-reported frequency of sinus infections and courses of CRS-related antibiotics and corticosteroids were used as a proxy for acute exacerbations in previous studies, it is not known how well these metrics account for all cases of AECRS. Moreover, these proxy measures for AECRS are all dependent on patient recall and, in some cases, practice patterns of the varying physicians (ie, who prescribe systemic medications for patients with CRS). It is very likely that there are cases of AECRS that patients would not describe as sinus infections or for which they do not take antibiotics or oral corticosteroids. These forms of AECRS, for which there are no current means to study, would not be accounted for in this study. Additionally, our data show a higher percentage of patients with aeroallergen hypersensitivity in the exacerbation-prone group relative to the no-exacerbation group (although not statistically significant); it is possible that misidentification of allergy flares as sinus infections may have contributed to patients falling into the exacerbation-prone phenotype. Moreover, it is possible that our metrics of AECRS may be biased toward specific subtypes of AECRS, which would bias our associations toward AECRS of that subtype. For example, although subtypes of
AECRS have not been formally defined, 2 of our AECRS metrics—sinus infection frequency and use of CRS-related antibiotics—may be reflective of bacterial AECRS; as such, it is possible that our associations may be more pertinent for patients having high-frequency bacterial AECRS.

**Conclusion**

CRS is a highly prevalent disease with significant associated QOL and productivity detriment as well as health care costs. A subset of patients with CRS is exacerbation prone, experiencing highly recurrent AECRS. These appear to be not only patients with a greater burden of nasal symptoms but also patients whose disease may cause greater cephalalgia. A better understanding of the characteristics that can identify patients with CRS who are exacerbation prone will help us determine the etiologies underlying AECRS, define better ways to prevent and treat AECRS and decrease its associated health care cost and utilization, and further improve patient outcomes.

**Author Contributions**

Katie M. Phillips, study design, data collection, data interpretation, manuscript preparation; Eric Barbarite, data acquisition and manuscript revising; Lloyd P. Hoehle, data acquisition and manuscript revising; David S. Caradonna, study design, data acquisition and manuscript design; Stacey T. Gray, study design, data acquisition and manuscript design; Ahmad R. Sedaghat, study design, data acquisition, data interpretation, manuscript revising.

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