慢性鼻竇炎急性發作頻率與氣喘控制的相關性

Relationship Between Chronic Rhinosinusitis Exacerbation Frequency and Asthma Control

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Commentary

[one airway, one disease], [unified airway disease], [common airway disease] 指的就是呼吸道是一個連續的構造，是我們人為將它分為上(鼻部)、下呼吸道(支氣管，肺部)；因此上下呼吸道的疾病，尤其是發炎疾病，常有較高的共病率，且會互相影響。慢性鼻竇炎與氣喘就是一例，透過血液中的發炎介子、鼻涕倒流中的發炎物質、自主神經反射(nasopharyngo-bronchial reflex)…等等影響呼吸道的另一區域。因此在治療這類病人時，需要上下呼吸道整體一起評估、一起治療，才能得到較好的效果。

先前的研究已經證實慢性鼻竇炎的嚴重程度與氣喘的控制程度相關。治療其中之一可以改善另外一個。如鼻竇內視鏡手術後可以改善氣喘控制，而氣喘共病是慢性鼻竇炎手術後復發的危險因子。而本篇研究則探討慢性鼻竇炎的急性發作頻率與氣喘控制程度的相關性。結果發現由病人回答其三個月內鼻竇感染、鼻竇炎相關抗生素使用、鼻竇炎相關口服類固醇使用的次數與氣喘控制測試分數(ACT)都呈現良好負相關。另外，三種 3 個月內鼻竇炎急性發作次數大於等於一次時，可以是氣喘控制不良(ACT<20)的偵測指標。這樣的研究結果再次強化我們對這群合併有氣喘與慢性鼻竇炎的病患，上下呼吸道需要一起評估和治療的必要性了。從表一也可以發現這群病人將近七成是有鼻瘜肉，超過一半接受過鼻竇手術，而其三個月內鼻竇炎急性發作平均還有 0.6~0.8 次，顯示這的確是相對難治的病患族群。

然而這個研究僅分析相關性，無法得知因果關係。因此從文章中我們無法知道這群病人是因為鼻竇炎急性發作造成氣喘控制不良，或者氣喘控制不良讓鼻竇炎急性發作，或者兩者都有。另外，氣喘控制測試是一個簡單，快速的主觀氣喘評估問卷工具，包含五個氣喘症狀及藥物使用的問題(每題 1-5 分，滿分 25 分)，在臨床上廣泛被使用。因此文章後半部分以鼻竇炎急性發作來預測氣喘控制不良的敏感度與特異度其實就有點畫蛇添足了。

其他關於本篇研究的限制性在文章裡都有提及，包括病人記憶的誤差，鼻竇炎、氣喘有些症狀重疊(如咳嗽)，只有主觀問卷評估沒有客觀檢查測量(每個病人感受度，耐受度不同)，橫斷性研究沒有介入治療之影響分析等等。

關鍵字：慢性鼻竇炎，急性發作，氣喘控制，22 項鼻及鼻竇結果測試，抗生素，口服類固醇
Relationship Between Chronic Rhinosinusitis Exacerbation Frequency and Asthma Control

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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 \( b = -1.2, 95\% \text{ confidence interval } [CI]: -2.3 \text{ to } -0.1, P = .033\)), CRS-related antibiotics courses (adjusted \( b = -1.4, 95\% \text{ CI: } -2.3 \text{ to } -0.5, P = .004\)), and CRS-related oral corticosteroid courses (adjusted \( b = -1.5, 95\% \text{ CI: } -2.5 \text{ to } -0.5, P = .004\)) 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.
The level of CRS symptom severity is negatively associated with the level of asthma control. 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. 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 CRS patients. 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. 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 smoker in the past was a smoker for this study. At enrollment, the evaluating physician for a history of asthma diagnosed based on consensus guidelines as smoker in the past was a smoker for this study. Data were collected at enrollment. Demographic information within the last 6 months were excluded. All participants were assessed by the evaluating physician for a history of asthma diagnosed based on consensus guidelines as smoker in the past was a smoker for this study.

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 corticosteroid 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 \(\hat{\beta} = -2.1\), 95% confidence interval [CI]: \(-3.1\) to \(-1.0\), \(P < .001\)), CRS-related antibiotics courses (\(\hat{\beta} = -1.2\), 95% CI: \(-2.1\) to \(-0.2\), \(P = .016\)), and CRS-related oral corticosteroid courses (\(\hat{\beta} = -1.6\), 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 (\(\hat{\beta} = -1.2\), 95% CI: \(-2.3\) to \(-0.1\), \(P = .033\)), CRS-related antibiotics courses (\(\hat{\beta} = -1.4\), 95% CI: \(-2.3\) to \(-0.5\), \(P = .001\)).
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 corticosteroids 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 three months provided 88.2% sensitivity with 62.2% specificity in detecting asthmatic CRS patients with poor asthma control.

![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.](image)

### Table I.
Characteristics of Study Participants.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study Participants, N = 108</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></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><strong>Comorbidities</strong></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><strong>Asthma characteristics</strong></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><strong>CRS characteristics</strong></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.

.004), and CRS-related oral corticosteroid courses (β = −1.5, 95% CI: −2.5 to −0.5, P = .004) in the last 3 months remained statistically significant. Thus, our
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
TABLE III.
Accuracy of CRS Disease Measures to Detect Poorly Controlled Asthma in Asthmatic CRS Patients.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Optimal Cutoff Value</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-reported number of sinus infections in the last 3 months</td>
<td>≥1</td>
<td>70.6%</td>
<td>47.3%</td>
</tr>
<tr>
<td>Patient-reported number of CRS-related antibiotic courses in the last 3 months</td>
<td>≥1</td>
<td>50.0%</td>
<td>73.0%</td>
</tr>
<tr>
<td>Patient-reported number of CRS-related oral corticosteroid courses in the last 3 months</td>
<td>≥1</td>
<td>58.8%</td>
<td>71.6%</td>
</tr>
<tr>
<td>SNOT-22 score</td>
<td>≥45</td>
<td>82.4%</td>
<td>67.6%</td>
</tr>
</tbody>
</table>

*Maximizes the sum of sensitivity and specificity.

CRS = chronic rhinosinusitis; SNOT-22 = 22 item Sinonasal Outcome Test.

epidemiological, clinical, and pathophysiologica associations between asthma and CRS. Previous work has epidemiologically linked CRS and asthma through the frequent comorbidity of these two diseases. Clinical, the unified airway, in relation to the effect of CRS on asthma, has been demonstrated beyond negative asthma outcomes driven by CRS. Numerous studies have also suggested that medical and surgical treatments for CRS not only lead to improvements in CRS, but to improvements in asthma status as well. In fact, the relationship between CRS and asthma is deemed to be so clinically relevant that the National Heart Blood and Lung Institute has made the precautionary recommendation to consider CRS as an exacerbating factor in asthmatics. The mechanisms underlying the interdependence of the upper and lower airways remain unknown. However, several studies have provided molecular insights into how AECRS may contribute to poor asthma control. Molecular profiling of nasal secretions of CRS patients in the midst of an AECRS has revealed a type 2 T-helper (Th2) cytokine-skewed profile, which may be evident systemically in the peripheral blood as well. That asthma exacerbations have also been associated with a Th2 response suggests that common inflammatory mechanisms, which can leak into the systemic circulation, may underlie how localized exacerbations could provoke mirroring symptomatological events diffusely throughout the airway, inciting new inflammatory events in other regions of the respiratory mucosa. Our results provide clinical evidence for this possible immunologic link between AECRS and asthma control.

Our findings may also have potentially important implications for evaluation and potentially treatment of asthma in CRS patients. As the relationship between asthma and CRS outcomes is increasingly found to be interdependent, our results provide a means for assessing asthma control in asthmatic CRS patients by querying CRS-related metrics. Additionally, although the goal of CRS treatments is a reduction in the clinical manifestations of CRS, our results and others showing the association between CRS symptom severity and asthma control, as well as previous studies demonstrating responsiveness of asthma to CRS treatments, may inform clinical decision making in the management of asthmatic CRS patients.

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.

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