Establishing validity of a novel patient-centered and directly measurable definition of acute exacerbation of chronic rhinosinusitis

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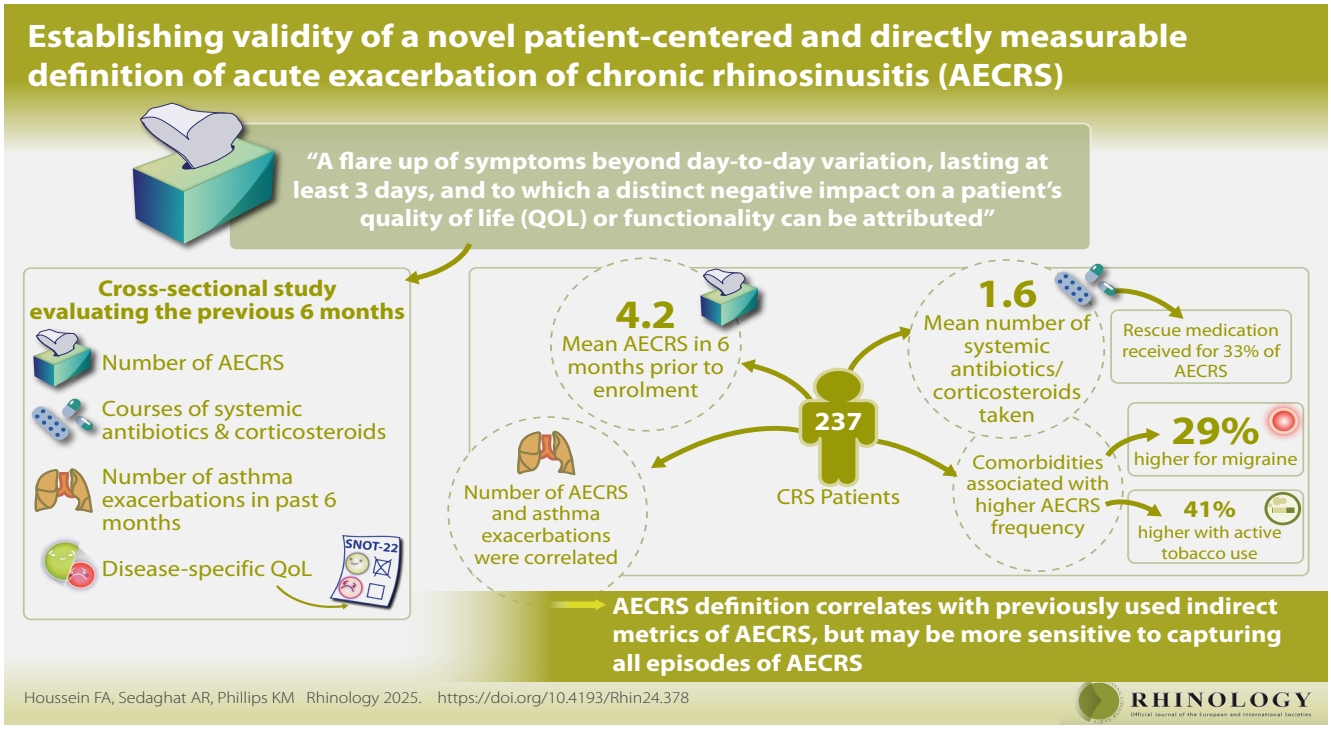
Rhinology 63: 5, 584 - 590, 2025

https://doi.org/10.4193/Rhin24.378



Abstract

Background: A patient-centered and directly measurable definition for acute exacerbation of chronic rhinosinusitis (AECRS) has been developed as "a flare up of symptoms beyond day-to-day variation, lasting at least 3 days, and to which a distinct negative impact on a patient's quality of life (QOL) or functionality can be attributed". Our aim is to understand how this definition correlates with previously used metrics. **Methodology**: Cross-sectional study of chronic rhinosinusitis (CRS) patients. The number of AECRS (using this novel definition), courses of CRS-related systemic antibiotics and corticosteroids taken for these AECRS, and number of asthma exacerbations in the past 6 months was queried. Disease-specific quality of life was measured using the 22-item Sinonasal Outcome Test. **Results**: A total of 237 CRS patients were enrolled. In the 6-month period prior to study enrollment, the mean number of AECRS was 4.2 while the mean number of systemic antibiotics or corticosteroids taken for these AECRS was 1.6 reflecting patients received rescue medication for 33% of AECRS. The number of AECRS was weakly correlated with number of systemic rescue medications and SNOT-22 score. For asthmatic CRS patients, numbers of AECRS and asthma exacerbations were correlated. Finally, comorbidities were associated with higher AECRS frequency by 29% in migraine and 41% in active tobacco users. **Conclusions**: We achieved our aim by showing the AECRS definition correlates with systemic rescue medication usage, disease-specific QOL and asthma exacerbations. Our results demonstrate that indirect measures of AECRS may not capture all AECRS. Furthermore, comorbid migraine and tobacco use are associated with AECRS frequency.

Key words: chronic rhinosinusitis, acute exacerbation of chronic rhinosinusitis, sinus infection, systemic antibiotics and oral steroids, patient-reported outcome

Introduction

Background

Chronic rhinosinusitis (CRS) is a heterogenous inflammatory condition of the sinonasal cavity impacting approximately 5-10% of the population [1-3]. Much like patients with asthma, the lower respiratory system correlate of CRS, patients with CRS experience acute exacerbations of their sinonasal symptoms. A recent study estimates approximately a quarter of CRS patients experience at least one acute exacerbation of chronic rhinosinusitis (AECRS) per year [4]. Furthermore, beyond the frequency with which patient's experience AECRS, patients also suffer a distinct quality of life (QOL) impact secondary to their AECRS above and beyond the QOL detriment caused by daily, baseline sinonasal symptomatology [5]. Despite the frequency and impact on patients, AECRS are relatively understudied and represent an opportunity for our field to learn more about this important phenomenon for the betterment of our patients. To better study AECRS, we must first use a precise definition to ensure that we study the same phenomenon in a prospective manner.

In the most recent European Position Statement on Rhinosinusitis and Nasal Polyps 2020, AECRS were defined as "worsening of symptom intensity with return to baseline CRS symptom intensity, often after intervention with corticosteroids and/or antibiotics [6]. "This definition was further expanded upon after qualitative inquiry with CRS patients to "a flare up of symptoms beyond day-to-day variation, lasting at least 3 days, and to which a distinct negative impact on a patient's QOL or functionality can be attributed [7,8]. "This modified definition incorporates real-world CRS patient input and also allows health care providers to diagnose an AECRS in real-time with specific criteria. Furthermore, with consensus around a single definition, the research community can better study the phenomenon of AECRS, more quickly advancing knowledge on this topic.

To move to consensus around this modified, comprehensive and patient-centered definition of AECRS further validation is needed.

Objective

How the modified definition correlates with previously used indirect metrics of AECRS is unknown. Therefore, the objective of our study is to evaluate the correlation of this modified definition of AECRS with previously used indirect proxy measures of AECRS and important metrics of CRS disease burden associated with AECRS.

Materials and methods

Setting

The study was conducted in a single tertiary care rhinology clinic from June 2023 to January 2024.

Participants

All participants provided informed consent to participate.Inclusion criteria were being equal to or over the age of 18, meeting consensus diagnostic guideline criteria for CRS [6] and willingness to participate in the study. To remove the confounding effects of evolution in CRS disease state and patient perceptions during the recovery period, patients with endoscopic sinus surgery within the last six months were excluded. Patients with comorbid vasculitis, cystic fibrosis, sarcoidosis and immunosuppression were also excluded.

Study design

This is a cross-sectional study. This study was approved by the University of Cincinnati Institutional Review Board. All data—including demographics, health information, physical exam findings and patient-reported outcome measures—were collected at enrollment.

Data sources

Demographic information, including age and gender, was obtained. A smoker was defined as any patient who currently smoked or reported a history of tobacco use [9,10]. 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 determined through formal allergy testing. Participants were interviewed to identify a history of migraine, previous sinus surgery or a history of aspirin sensitivity. The presence of nasal polyps and history of prior sinus surgery were confirmed on nasal endoscopy.

Participants were then queried on the frequency of AECRS in the past 6 months as the primary outcome of interest (defined as the dependent variable). AECRS was specifically defined for participants as:

A flare up of symptoms beyond day-to-day variation, lasting at least 3 days, and to which a distinct negative impact on a patient's quality of life (QOL) or functionality can be attributed.

Additionally, participants were asked how many asthma exacerbations they had experienced in the past 6 months which were caused by an AECRS. Furthermore, they were queried on how many courses of oral steroids and antibiotics they had received for an AECRS in the past 6 months (which had previously been used as an indirect proxy for an AECRS). Finally, all participants completed the 22-item Sinonasal Outcome Test (SNOT-22), as a reflection of CRS-specific QOL [11], and the 5-dimension EuroQol questionnaire, from which the visual analog scale (EQ5D-VAS) was used, as a reflection of general-health related QOL [12,13].

The SNOT-22 and EQ5D-VAS were collected to understand the burden of disease in each patient.

Table 1. Correlation between frequency of AECRS and metrics of CRS disease burden over a 6-month period † for the Total Cohort.

Variables	Mean, μ	SD, σ	Correlation, ρ
AECRS frequency over 6-month period †	4.2	4.8	
Rescue medications use over 6-month period ‡	1.6	1.9	0.27
SNOT22 Total	45.1	21.4	0.29
EQ5D-VAS	66.8	21.1	-0.12
Age, years	50.6	16.2	-0.10

† AECRS frequency over 6-month period truncated at ≤ 25 observations. ‡ Correlation with AECRS frequency over 6-month period truncated at ≤ 25 observations and AECRS medications use over 6-month period truncated at ≤ 10. Abbreviations: Acute exacerbation of Chronic Rhinosinsuitis (AECRS), 22 Item Sinonasal Outcomes Test (SNOT22), 5-dimension EuroQol questionnaire visual analog scale (EQ5D-VAS).

Table 2. Correlation between frequency of AECRS and metrics of CRS disease burden over a 6-month period † for the Asthma Cohort.

Variables	Mean, m	SD, s	Correlation, ρ
AECRS frequency over 6-month period †	4.0	4.2	
Rescue medications use over 6-month period ‡	1.8	2.0	0.29
SNOT22 Total	48.1	21.8	0.29
EQ5D-VAS	64.8	20.9	-0.01
Asthma exacerbations over 6-month period	1.4	2.2	0.25
Age, years	46.4	16.9	-0.17

† AECRS frequency over 6-month period truncated at ≤ 25 observations. ‡ Correlation with AECRS frequency over 6-month period truncated at ≤ 25 observations and AECRS medications use over 6-month period truncated at ≤ 10. Abbreviations: Acute exacerbation of Chronic Rhinosinsuitis (AECRS), 22 Item Sinonasal Outcomes Test (SNOT22), 5-dimension EuroQol questionnaire visual analog scale (EQ5D-VAS).

Variables of interest

The primary outcome was the frequency of AECRS as measured by the newly adopted definition. We then wanted to understand the correlation of the frequency of AECRS with burden of disease metrics in CRS to understand if the frequency of AECRS appropriately correlates with disease severity. Next, we evaluated the correlation of frequency of AECRS to previously used indirect proxies of AECRS (such as number of systemic rescue medications used for CRS). Finally, we looked at factors associated with increasing frequency of AECRS to further understand defining characteristics of this phenomenon.

Study size

Our recruitment goal was at least 200 participants so we could have a power of 0.8 at a significance level of 0.05 to detect an association of at least moderate effect size between indirect proxy measures of AECRS and the modified AECRS definition, while controlling for confounders.

Statistical analysis

First a standardized normal probability plot was used to determine if the continuous variables were normally distributed. If not, then outliers were removed to make the distribution normal. To understand how indirect metrics of AECRS correlated with the modified definition of AECRS, means, standard deviations, and correlations where then determined on the normally distributed variables. Poisson regression was used to find the association between the frequency of AECRS as defined by the modified definition for a six-month period and possible predictor variables which included allergic rhinitis, migraine, tobacco status, gender, polyp status, asthma status and AERD. Poisson methods were used since ACERS at 6 months is a count variable and its mean and standard deviation values were similar. All analyses were done using Stata/SE 18.5.

Results

Participants

A total of 237 participants, 57 (24.1%) with CRS with nasal polyps (CRSwNP) and 180 with CRS without nasal polyps (CRSsNP) were recruited.

Descriptive data

Gender was reported as female by 131 (55.3%) participants, male by 104 (43.9%), and non-binary by 2 (0.8%), and the

Table 3. Association between frequency of AECRS and characteristics of interest over a 6-month period † for the Total Cohort.

Variables	IRR	95% CI	p-value	Count, N
Female vs. Male	0.87	0.64 – 1.18	0.377	124/99
CRSwNP vs. CRSsNP	1.03	0.70 – 1.52	0.887	53/172
Asthma vs. No Asthma	0.96	0.71 – 1.30	0.791	85/140
AR vs. No AR	1.27	0.90 – 1.74	0.148	127/98
AERD vs. No AERD	0.85	0.35 – 2.10	0.731	3/222
Tobacco vs. No Tobacco	1.41	0.99 – 1.99	0.056	48/177
Migraine vs. No Migraine	1.29	0.95 – 1.75	0.103	77/148

† AECRS frequency over 6-month period truncated at ≤ 25 observations. ‡ Correlation with AECRS frequency over 6-month period truncated at ≤ 25 observations and AECRS medications use over 6-month period truncated at ≤ 10. Abbreviations: Acute exacerbation of Chronic Rhinosinsuitis (AECRS), 22 Item Sinonasal Outcomes Test (SNOT22), 5-dimension EuroQol questionnaire visual analog scale (EQ5D-VAS).

Table 4. Association between frequency of AECRS and characteristics of interest over a 6-month period † in the Asthma Cohort.

Variables	IRR	95% CI	p-value	Count, N
Female vs. Male	0.86	0.53 – 1.42	0.562	53/32
CRSwNP vs. CRSsNP	1.20	0.68 – 2.12	0.524	24/61
AR vs. No AR	1.14	0.67 – 1.93	0.625	60/25
AERD vs. No AERD	0.87	0.35 – 2.19	0.774	3/82
Tobacco vs. No Tobacco	1.68	1.00 – 2.81	0.050	21/64
Migraine vs. No Migraine	1.64	1.06 – 2.55	0.028	36/49
Migraine vs. No Migraine	1.29	0.95 – 1.75	0.103	77/148

† AECRS frequency over 6-month period truncated at ≤ 25 observations. Abbreviations: Chronic rhinosinusitis with nasal polyps (CRSwNP), Chronic rhinosinusitis without nasal polyps (CRSsNP), Allergic rhinitis (AR), Aspirin exacerbated respiratory disease (AERD).

participants had a mean age of 50.6 (SD=16.2) years. Of the participants, 37.1% (n = 88) had a history of asthma and 55.2% (n = 131) had a history of allergic rhinitis (AR). A minority of participants (1.7%, n = 4) had a history of aspirin sensitivity (AERD) or of tobacco use (20.3%, n = 48). 34.6% (n = 82) of participants reported a history of migraines. The mean SNOT-22 score was 45.1 (SD = 21.4), and mean EQ5D-VAS score was 66.8 (SD = 21.1).

In the total cohort, AECRS frequency correlates with CRS burden of disease metrics and previously used indirect proxies for AECRS

Overall, participants experienced 4.2 (SD = 4.8) AECRS in the last six months and received a mean of 1.6 (SD = 1.9) AECRS-related systemic antibiotic or corticosteroid courses (Table 1). We observed that the number of AECRS was weakly correlated with the number of systemic medications (ρ=0.27) patients received as well as with their disease specific QOL, measured via SNOT-22 scores (ρ =0.29, Table 1). AECRS were similarly weakly correlated with number of asthma exacerbations (ρ =0.27).

In the asthma cohort, AECRS frequency correlates with CRS burden of disease metrics and previously used indirect proxies for AECRS

We then analyzed AECRS frequency with the same factors among asthmatic participants specifically. Asthmatic participants experienced a mean of 4.0 (SD=4.2) AECRS, requiring a mean of 1.8 (SD=2.0) courses of CRS-related systemic antibiotic or corticosteroids (Table 2). These participants also experienced a mean of 1.4 (SD=2.2) asthma exacerbations during this time (Table 2). As was the case for the entire cohort, the number of AECRS was directly correlated with antibiotic or corticosteroid courses received (ρ =0.29), as well as SNOT-22 score (ρ=0.29) and number of asthma exacerbations (ρ=0.25, Table 2).

Factors associated with AECRS frequency among total cohort

We next sought to analyze factors that may be associated with increased frequency of AECRS. A history of AR, migraine and tobacco use showed a trend towards significance. AR was associated with a 27% higher incidence rate of AECRS Incidence rate ratio (IRR): 1.27, 95%CI: 0.90-1.74, p=0.148). Migraine was found to have a 29% higher incidence rate of AECRS (IRR: 1.29,

95%CI: 0.95-1.75, p=0.103, Table 3). Tobacco use was found to be the most strongly associated with increased AECRS with an associated 41% increase in frequency (IRR: 1.41, 95%CI: 0.99-1.99, p=0.056, Table 3).

Factors associated with AECRS frequency among the asthma cohort

When analyzing the same factors among asthmatic CRS patients specifically, migraine and tobacco use were again significantly associated with increasing AECRS frequency. Migraine history was associated with a 64% higher number of AECRS (IRR: 1.64, 95%CI: 1.06-2.55, p=0.049), and tobacco use was associated with a 68% percent increase (IRR: 1.68, 95%CI: 1.00-2.81, p=0.028, Table 4). As seen in the total cohort, AR (IRR: 1.14, 95%CI: 0.67-1.93, p=0.625) sex (IRR: 0.86, 95%CI: 0.53-1.42, p=0.562), polyp status (IRR: 1.20, 95%CI: 0.68-2.12, p=0.524), and AERD history (IRR: 0.87, 95%CI: 0.35-2.19, p=0.774), were not associated with AECRS frequency (Table 4).

Discussion

Key results

We found that CRS participants, on average, reported about 4 episodes of AECRS in the previous six months. We also found increased AECRS frequency was weakly correlated with increased usage of systemic rescue medications and increased frequency of asthma exacerbations, a finding in line with the known association between asthma and CRS [15]. Furthermore, AECRS frequency was correlated with the SNOT-22 score, reflecting an overall negative effect on disease-specific quality of life. When specifically studying CRS patients with comorbid asthma, we similarly found AECRS frequency to be correlated with rescue medication usage, SNOT-22 score, and frequency of asthma exacerbations.

Interpretation

Our results can be used to inform how frequently CRS patients experience AECRS and how this impacts systemic rescue medication usage, sinonasal symptomatology and patient reported outcome measures. AECRS have a significant QOL impact on CRS patients but remain relatively understudied [5,14]. In the most recent European Position Statement on Rhinosinusitis and Nasal Polyps 2020, AECRS were defined as "worsening of symptom intensity with return to baseline CRS symptom intensity, often after intervention with corticosteroids and/or antibiotics [6]." This definition was further expanded upon after quality inquiry with CRS patients to "a flare up of symptoms beyond day-to-day variation, lasting at least 3 days, and to which a distinct negative impact on a patient's QOL or functionality can be attributed [7,8]." While a modified, comprehensive and patient-centered definition of AECRS has allowed providers to directly measure AECRS, investigations to fully validate this new AECRS definition is ongoing. It has remained unclear how quantifying AECRS with this new definition correlates with metrics of CRS disease burden and in this study, we sought to address this knowledge gap. While the modified, patient-centered and evidence-based definition of AECRS was found to correlate with the need for systemic rescue medications (antibiotics and corticosteroids), which has previously been used as indirect proxy measures of AECRS, the mean number of AECRS experienced by patients was greater than the mean usage of rescue medications, suggesting that commonly used proxy measures of AECRS may not adequately capture all AECRS events. When reflecting on the definition of AECRS which describes escalation in sinonasal symptoms for greater than 3 days with a QOL or functional impact, this is certainly not specific to a bacterial etiology and instead may have several different catalysts such as allergic, neurogenic, or other exacerbations of the inflammatory system such as an asthma exacerbation. Therefore, while the previously used indirect measurements of AECRS may have captured severe flares which had required oral antibiotics or corticosteroids—and it is important to note that the use of these medications can also be influenced by patient and provider preference—this modified AECRS definition has a broader catchment which more accurately reflects the burden AECRS inflicts on patients.

After demonstrating the relationship between AECRS and previous indirect measures, we went on to describe the effect several comorbidities may have on AECRS frequency. The incidence of AECRS occurring in a 6-month period is higher among those with comorbid allergic rhinitis, migraine, and tobacco users. Furthermore, in those with comorbid asthma, there were statistically significant associations between AECRS frequency over a 6-month period and a diagnosis of migraine or use of tobacco. These associations were stronger for asthmatic participants specifically than for the total CRS cohort. These comorbid relationships may give us further insight into etiologies of AECRS or serve as a mimic of an AECRS. Nonetheless, those with comorbid migraine and tobacco use may be worth exploring as we study this phenomenon in more detail in the future.

Our results serve to further justify the use of the patient-centered, evidence-based definition of AECRS as a more sensitive means to capture episodes of AECRS.

Indirect proxy measures reflecting the need for systemic rescue medications may simply underestimate AECRS frequency. Finally providing a prospective, definition allows researchers to study the same phenomenon allowing further study and insight on this topic.

Limitations

Our results should be interpreted within the constraints of the study's limitations. While the modified definition of AECRS requires at least 3 days of symptom flare up, it does not incorporate a maximum length of time to differentiate an AECRS

from disease progression or recurrence. At present there is no evidence to temporally distinguish when a perceived AECRS truly reflects disease progression or recurrence. However, based on a previous study utilizing qualitative interviews with patients, we believe that the phrasing of this AECRS definition as a "flare up beyond normal day-to-day variation" indicates the rapid and acute nature of AECRS rather than reflecting—the often gradual—progression or recurrence of disease. Patients in this cohort were asked to recall how many AECRS they had experienced and how many systemic medications they had taken for their CRS over a 6-month period and are subject to recall bias. Furthermore, all participants included in this study were seen at a tertiary care referral clinic of a singular health system, and similar studies will need to be performed in other regions and systems to ensure the universal generalizability of these results. Finally, recruitment from a tertiary care institution introduces a potential source of bias as this clinic is more likely to see more severe disease.

Generalisability

The definition of AECRS as "a flare up of symptoms beyond day-to-day variation, lasting at least 3 days, and to which a distinct negative impact on a patient's quality of life (QOL) or functionality can be attributed" is specific, measurable, patient-centered, evidence-based definition which reflects multiple metrics of CRS disease burden including the need for systemic rescue medication usage, CRS-specific QOL, and asthma exacerbation. Previously used indirect proxy measures to measure AECRS do not capture all AERCS as measured by this modified definition. Furthermore, tobacco use and migraine history are significantly associated with AECRS among CRS patients with comorbid asthma.

Conclusion

Utilizing the previously defined definition of AECRS - "a flare up of symptoms beyond day-to-day variation, lasting at least 3 days, and to which a distinct negative impact on a patient's quality of life (QOL) or functionality can be attributed" - we found this correlates with systemic rescue medication usage, disease-specific QOL and asthma exacerbations. Our results demonstrate that indirect measures of AECRS may not capture all AECRS. Furthermore, comorbid migraine and tobacco use are associated with AECRS frequency.

Acknowledgements

Not applicable.

Authorship contribution

FAH: collection of data, interpretation of results, write up of manuscript, critical review of all contents. ARS collection of data, statistical analysis, interpretation of results, write up of manuscript, critical review of all contents. KMP concept of study, study design, collection of data, statistical analysis, interpretation of results, write up of manuscript, critical review of all contents.

Conflict of interest

None.

Funding

None.

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Rhinology 63: 5, 584 - 590, 2025
https://doi.org/10.4193/Rhin24.378

Received for publication:
August 27, 2024
Accepted: May 4, 2025

Associate Editor:
Michael Soyka