Clinical factors associated with acute exacerbations of chronic rhinosinusitis

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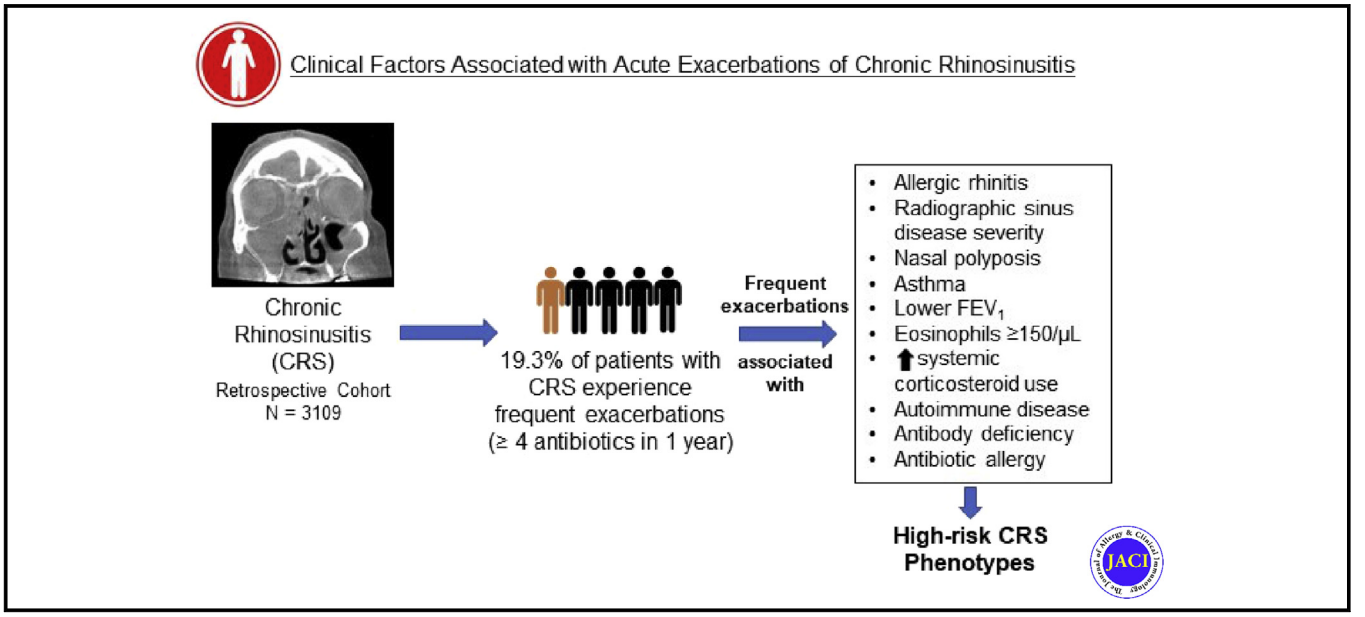
GRAPHICAL ABSTRACT



Background: Chronic rhinosinusitis (CRS) is complicated by frequent acute exacerbations leading to significant health care burden and impaired quality of life.

Objective: The objective of this study was to identify clinical factors associated with frequent acute exacerbation of CRS (AECRS).

Methods: This is a retrospective cohort study of patients with CRS from January 1, 2014, to May 31, 2016. Frequent AECRS was defined as at least 4 episodes over a 12-month period in which an antibiotic was prescribed for worsening sinus symptoms, and infrequent AECRS was defined as 0 to 3 episodes. Clinical factors, including asthma, allergic rhinitis, eosinophil count of at least 150 cells per microliter, and autoimmune disease, were evaluated for associations between the 2 groups.

Results: Of the 3109 patients with CRS who were identified, 600 (19.3%) were classified as having frequent exacerbation. Asthma, allergic rhinitis, eosinophil count of at least 150 cells per microliter, and autoimmune disease were associated with frequent AECRS with statistically significant adjusted odds ratios (aORs) after controlling for age, race, and sex in multivariate analysis (asthma aOR = 2.61 [95% CI = 2.14-3.18]; allergic rhinitis aOR = 1.96 [95% CI = 1.58-2.42]; eosinophil count of at least 150 cells per microliter aOR = 1.54 [95% CI = 1.21-1.97]; and autoimmune disease aOR = 1.68 [95% CI = 1.36-2.07]). Antibody deficiency, antibiotic allergy,

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lower FEV_1, radiographic sinus disease severity, nasal polyposis, and systemic corticosteroid use were also associated with frequent AECRS.
Conclusion: Patients with frequent episodes of AECRS were characterized by a higher prevalence of asthma, allergic rhinitis, eosinophil count of at least 150 cells per microliter, autoimmune disease, and other allergic and immunologic diseases. These findings identify a high-risk phenotype of patients with CRS for preventive interventions to reduce exacerbation frequency. (J Allergy Clin Immunol 2020;145:1598-605.)

Key words: *Chronic rhinosinusitis, exacerbation, antibiotics, asthma, allergic rhinitis, eosinophils, autoimmune disease*

Chronic rhinosinusitis (CRS) is a chronic inflammatory condition of the nose and paranasal sinuses with clinical symptoms of rhinorrhea, nasal congestion, sinus pressure and/or pain, and decreased sense of smell lasting for 12 weeks or longer. The prevalence of CRS has been estimated as 6% to 12% of the US population,[1,2] and the economic burden of this disease has been estimated to be between $60.2 and $64.5 billion US dollars in 2011, with a large proportion of that amount spent on office-based care and outpatient medications.[3] Patients with CRS experience significant reductions in quality of life (QOL) as a result of their symptoms,[4] and patient-perceived failure of symptom control has been associated with productivity loss.[5]

In addition to having chronic baseline symptoms, patients with CRS have acute episodes of worsening sinonasal symptoms that often resolve back to baseline following medical treatment.[2] The specific number of such flares annually, defined as acute exacerbation of CRS (AECRS), is unknown but is likely to be highly variable among all patients with CRS. Furthermore, treatments of AECRS typically include the use of antibiotics, and in patients with recurrent episodes of AECRS, this raises concern for adverse events due to frequent antibiotic use, such as the development of drug allergies and/or drug resistant organisms.[2,6]

Improved understanding of which patients with CRS are at greatest risk for frequent exacerbations could identify a patient population that would benefit from advanced therapies to potentially reduce frequency of AECRS and the associated antibiotic use and overall morbidity. In this retrospective study, we first determined the frequency of AECRS in our clinical cohort by identifying those patients with CRS who received an antibiotic prescription for worsening sinus symptoms over the course of a year. We then evaluated whether certain clinical factors distinguished patients with CRS who were experiencing frequent acute exacerbations from those who did not.

Abbreviations used
AECRS: Acute exacerbation of chronic rhinosinusitis
BMI: Body mass index
CRS: Chronic rhinosinusitis
CRSwNP: Chronic rhinosinusitis with nasal polyps
CT: Computed tomography
EMR: Electronic medical record
ICD-9: International Classification of Diseases, Ninth Revision
QOL: Quality of life

METHODS

Identification of subjects

This was a retrospective cohort study in which data were obtained from the electronic medical record (EMR) at Northwestern University clinics via the Enterprise Database Warehouse (EDW). Patients were included for analysis if they (1) had International Classification of Diseases, Ninth Revision (ICD-9), diagnosis codes of sinusitis (acute sinusitis 461.x or chronic sinusitis 473.x), (2) had a sinus computed tomography (CT) scan demonstrating sinomucosal inflammation at any point in their clinical history, and (3) had been evaluated in either the otolaryngology or allergy and immunology clinics at Northwestern University (Fig 1). CRS was diagnosed in accordance with leading consensus guidelines, and patients were excluded from the cohort if they did not have baseline chronic sinus symptoms and evidence of sinus disease on CT scan, effectively excluding patients with recurrent acute rhinosinusitis and acute sinusitis.[2] Patients were excluded from the study if they had an ICD-9 diagnosis code for cystic fibrosis. Data were analyzed for patients seen between January 1, 2014, and May 30, 2016. Demographic information, including age, sex, race, ethnicity (Hispanic versus non-Hispanic), body mass index (BMI), and smoking status was obtained. There were no age exclusions in this study; however, because the study population comprised patients of a tertiary adult care hospital, all patients were 18 years or older.

An acute exacerbation of CRS was defined as having received an antibiotic prescription for worsening sinus symptoms. Antibiotic prescriptions were identified in the EMR and then independently reviewed by the study investigators to confirm that each antibiotic was given for the indication of AECRS. Episodes in which antibiotics were prescribed for non–sinus-related symptoms or conditions were excluded from the analysis. Additional antibiotic courses utilized for the same exacerbation were excluded from the analysis. We defined patients with frequent AECRS as those who received 4 or more antibiotic prescriptions for their acute exacerbations over the course of any 12-month period during the study period. In contrast, those patients with CRS who received 0 to 3 antibiotic prescriptions for CRS were classified as having infrequent AECRS. The cutoff of 4 prescriptions was selected on the basis of the definition of recurrent acute rhinosinusitis from expert consensus rhinosinusitis guidelines.[2]

Identification of asthma, allergic rhinitis, and eosinophil count of at least 150 cells per microliter

The presence of asthma and allergic rhinitis was assessed via ICD-9 diagnosis codes 493.x and 477.x, respectively. FEV_1 percent predicted from either clinic spirometry or formal pulmonary function testing was determined from the patients' charts during the study period and utilized to categorize their asthma as either mild (>80 percent predicted), moderate (60-80 percent predicted), or severe (<60 percent predicted) in accordance with guidelines from the National Heart Lung and Blood Institute.[7] Peripheral absolute eosinophil counts from complete blood cell counts with differentials and total IgE levels during the study period were obtained for analysis. Eosinophil count was analyzed as both a continuous variable and a categoric variable by using at least 150 cells per microliter as a cutoff for analysis.

Identification of CRS phenotypes and severity

Sinus CT scans completed at any point in each patient's clinical history were reviewed and categorized as mild, moderate, or severe disease by the institution's neuroradiologist.[8] Nasal polyposis was determined via ICD-9 diagnosis code. Previous sinus surgery was determined by Current Procedural Terminology codes and the distinct encounter dates associated with these codes (30110, 30115, 31254, 31255, 31256, 31267, 31276, 31287, 31288, 31296, or 31297). The number of systemic corticosteroid prescriptions was obtained from the EMR. Although systemic corticosteroids were given for respiratory infections, it was frequently difficult to determine whether these medications were given for upper versus lower airway symptoms or both.

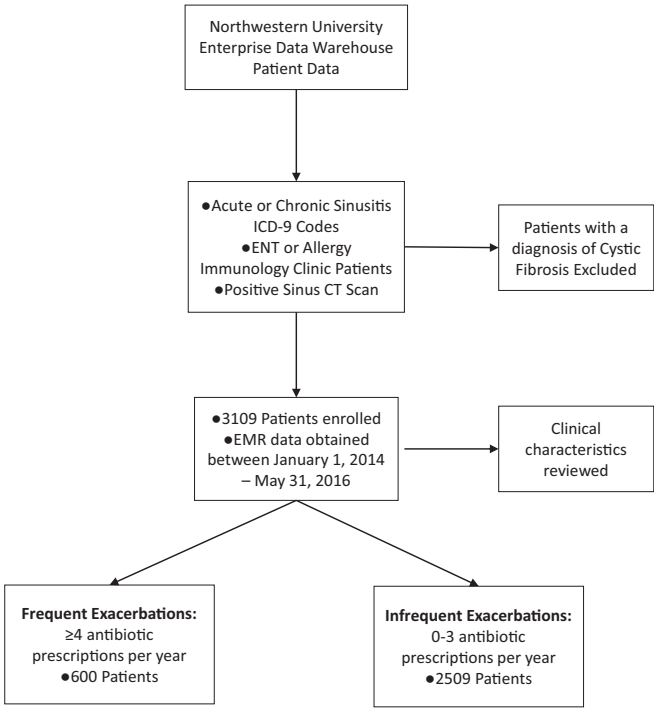

FIG 1. Algorithm for selecting patients with frequent versus infrequent AECRS. *ENT,* Ear, nose, and throat.

For analysis, we included a variable of any systemic corticosteroid prescription during the study period as well as a variable to compare the absolute numbers of systemic corticosteroid prescriptions between the 2 groups.

Identification of autoimmune disease and antibody deficiency

Autoimmune disease was a categoric variable in the analysis and considered positive if any of the following conditions identified via ICD-9 diagnosis codes were present: SLE, rheumatoid arthritis, hypothyroidism, thyroiditis, myasthenia gravis, multiple sclerosis, type I diabetes mellitus, Crohn disease, ulcerative colitis, psoriasis, pemphigus, pemphigoid, ankylosing spondylitis, Sjögren syndrome, idiopathic thrombocytopenic purpura, Raynaud phenomenon, chronic urticaria, and polymyalgia rheumatica. Quantitative immunoglobins (total IgG, IgM, and IgA levels) checked during the study period were obtained for analysis when available in the EMR. Immunoglobulins were considered consistent with hypogammaglobulinemia if the patients' IgG level was less than 600 mg/dL, their IgM level was less than 35 mg/dL, or their IgA level was less than 28 mg/dL. Specific antibody deficiency was defined as 50% of *Streptococcus pneumoniae* titers less than 1.3 μg/mL at least 4 to 6 weeks after vaccination with 23-valent pneumococcal polysaccharide.

Identification of drug allergy

The presence of any drug allergy or antibiotic allergy for each patient was obtained from the drug allergy section of the EMR.

Study end points

The present study examined associations between frequent AECRS episodes and the following factors: asthma, allergic rhinitis, eosinophil count of at least 150 cells per microliter, autoimmune disease, age, sex, race, ethnicity, smoking status (current, former, or never), BMI, any drug allergy, antibiotic allergy, nasal polyposis, sinus surgery, sinus CT scan severity, total systemic corticosteroid prescriptions, any systemic corticosteroid prescription, FEV_1 percent predicted, asthma severity based on FEV_1 percent predicted, hypogammaglobulinemia, specific antibody deficiency, and total IgE. Of these factors, asthma, allergic rhinitis, eosinophil count of at least 150 cells per microliter, and autoimmune disease were variables of particular interest; therefore, logistic regression analysis was performed to control for age, race, and sex as potential confounders.

TABLE I. Clinical characteristics

Characteristic	Frequent exacerbation group (n = 600)	Infrequent exacerbation group (n = 2509)	*P* value
Age (y) ± SEM	50.0 ± 15.0	49.0 ± 15.6	.178
Sex, no. (%)			
Male	220 (36.7)	1063 (42.4)	.012
Female	380 (63.3)	1446 (57.6)	
Race, no. (%)			
White	343 (63.6)	1471 (69.6)	.011
Black	57 (10.6)	221 (10.4)	
Other	139 (25.8)	423 (20.0)	
Hispanic, no. (%)	38 (7.0)	145 (6.9)	.985
BMI ± SEM	28.3 ± 6.6	27.6 ± 7.2	.030
Smoking, no. (%)			
Current	24 (4.0)	109 (4.4)	.883
Former	164 (27.3)	666 (26.6)	
Never	412 (68.7)	1729 (69.0)	

Statistical analysis

The Pearson chi-square test of independence was used for comparisons between the different patient groups regarding asthma, allergic rhinitis, eosinophil count of at least 150 cells per microliter, sinus CT scan severity, any systemic corticosteroid prescription, sinus surgery, nasal polyposis, asthma severity based on FEV_1 percent predicted, autoimmune disease, hypogammaglobulinemia, antibody deficiency, antibiotic allergy, drug allergy, sex, race, ethnicity, and tobacco use. The Wilcoxon rank sum test was used for comparisons between the different patient groups regarding total IgE and total number of systemic corticosteroid prescriptions. Simple logistic regression was used for comparisons between the 2 patient groups and absolute eosinophil counts. The Student 2-sample *t* test was used for comparisons between the different patient groups regarding age and BMI. Missing data were excluded from the analysis. Adjusted odds ratios with 95% confidence intervals were calculated via logistic regression analysis for associations between frequent AECRS episodes and asthma, allergic rhinitis, eosinophil count of at least 150 cells per microliter, and autoimmune disease after controlling for age, race, and sex. A *P* value less than .05 was utilized to define statistical significance. R statistical programming software, version 3.5.1, was utilized for the statistical analysis. Statistical programming support was provided by the Biostatistician Collaboration Center at the Northwestern University Feinberg School of Medicine.

This research was approved by the institutional review board of the Northwestern University Feinberg School of Medicine.

RESULTS

Demographics

With use of our algorithm, 3109 patients with CRS were evaluated at our tertiary care institution between January 1, 2014, and May 31, 2016 (Fig 1). Of these 3109 patients, 600 were classified as having frequent episodes of AECRS (19.3%) and 2509 were classified as having infrequent episodes of AECRS (80.7%) (Fig 1). There was no statistically significant difference in age between the 2 groups, each with a mean age of

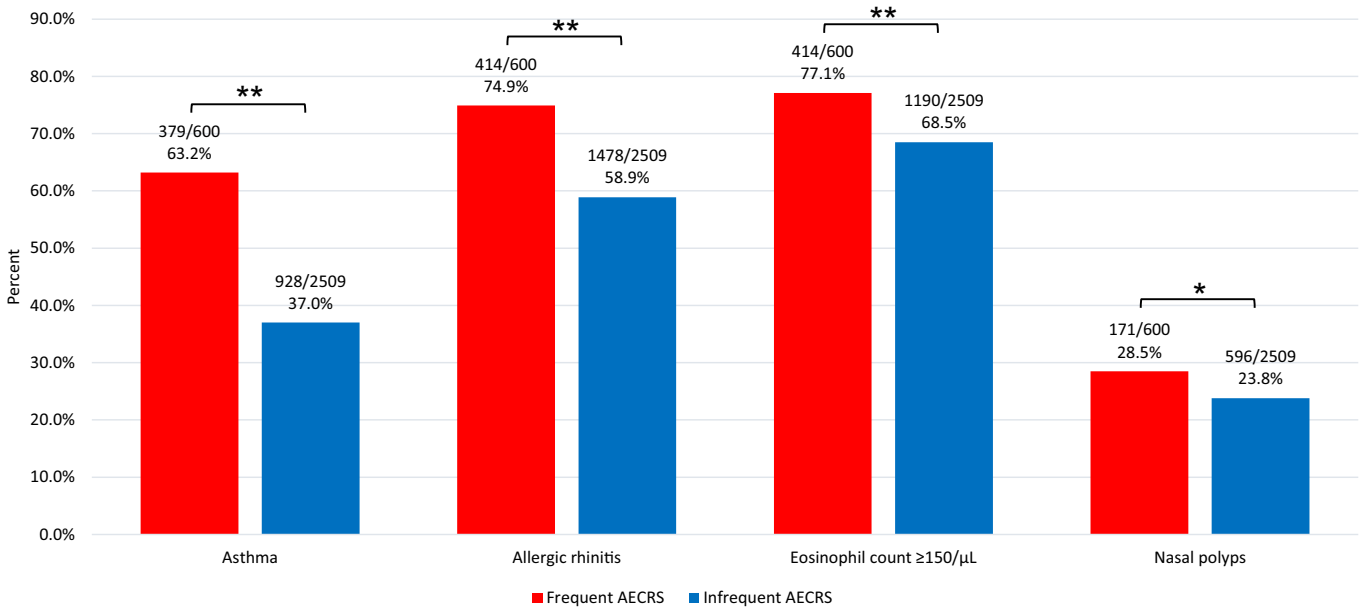

FIG 2. Clinical associations between asthma, allergic rhinitis, eosinophil count of at least 150 cells per microliter, and nasal polyps with frequent AECRS. *P = .018; **P < .001. P values calculated using the Pearson chi-square test.

approximately 50 years (Table I). In all, 58% of the cohort was female, and there was a significant association between female sex and frequent AECRS (P = .012). The majority of patients in the cohort were white, but there was an association between nonwhite race and the frequent AECRS group. Although the entire cohort had a mean BMI in the overweight category based on National Institutes of Health classifications, there was an association between higher BMI and frequent AECRS (P = .03).

Asthma, allergic rhinitis, and eosinophil count of at least 150 cells per microliter

Asthma, allergic rhinitis, and eosinophil count of at least 150 cells per microliter were each associated with frequent episodes of AECRS (Fig 2). Patients with frequent episodes of AECRS also had greater asthma severity as determined by FEV_1 percent predicted values (Fig 3). Specifically, when severe asthma was analyzed as a separate variable, it was associated with frequent episodes of AECRS. Asthma, allergic rhinitis, and eosinophil count of at least 150 cells per microliter maintained an association with frequent episodes of AECRS after control for age, race, and sex (Table II). When absolute eosinophil counts were analyzed as a continuous variable, higher absolute eosinophil counts showed an association with frequent AECRS (adjusted odds ratio = 1.32; 95% CI = 1.15-1.52; P <.001) (n = 2275). Total IgE levels were not statistically different between the 2 groups (for frequent episodes of AECRS, the level was 77.8 kU/L [median interquartile range = 19.40-327.00], whereas for infrequent episodes, the level was 113.00 kU/L [median interquartile range = 25.50-399.00]; P = .414) (n = 192).

CRS phenotype and severity

Patients with frequent episodes of AECRS had greater sinus disease severity, as determined by sinus CT scans (Fig 3). Any systemic corticosteroid use was associated with frequent episodes of AECRS. Specifically, patients experiencing frequent episodes of AECRS received significantly more systemic corticosteroid prescriptions during the study period as compared with those in the infrequent group (3.91 ± 4.51 versus 1.07 ± 1.85; P <.001). Patients with frequent episodes of AECRS were more likely to have nasal polyposis (Fig 2) and a history of sinus surgery (266 patients (44.3%) with frequent episodes versus 813 patients (32.4%) with infrequent episodes; P <.001).

Autoimmune disease and antibody deficiencies

Autoimmune disease and specific antibody deficiency were associated with frequent episodes of AECRS (Fig 4). Autoimmune disease maintained an association with frequent episodes of AECRS after control for age, race, and sex (Table II). There was a trend toward higher prevalence of hypogammaglobulinemia in the group with frequent AECRS; however, this trend was not statistically significant (53 of 305 patients (17.4%) with frequent episodes versus 84 of 646 patients (13.0%) with infrequent episodes; P = .085).

Drug allergy

Any drug allergy or antibiotic allergy was more frequently reported by patients with frequent AECRS versus by patients with infrequent AECRS (Fig 5).

DISCUSSION

This large cohort study found that patients with frequent episodes of AECRS were significantly more likely to have asthma, allergic rhinitis, an eosinophil count of at least 150 cells per microliter, autoimmune disease, and specific antibody deficiency as compared with patients with infrequent episodes of AECRS. This study also found that compared with patients experiencing infrequent episodes of AECRS, patients with

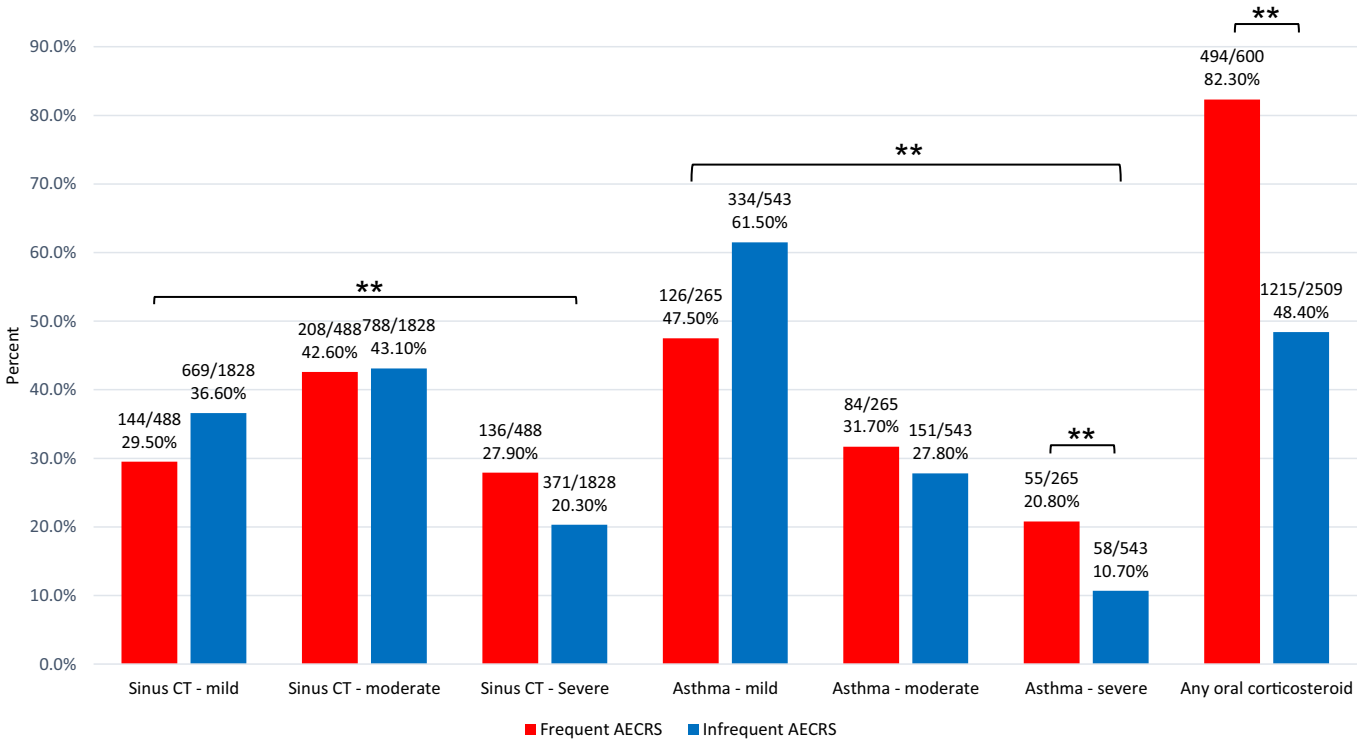

FIG 3. Upper and lower airway disease severity associations with frequent AECRS. $^{**}P < .001$ (calculated using the Pearson chi-square test).

TABLE II. Multivariable logistic regression analysis for primary outcome variables after controlling for age, race, and sex

Variable	Adjusted odds ratio	95% CI
Asthma	2.61	2.14-3.18
Allergic rhinitis	1.96	1.58-2.42
Eosinophil count ≥150/μL	1.54	1.21-1.97
Autoimmune disease	1.68	1.36-2.07

frequent episodes of AECRS had greater upper and lower airway disease severity as determined by increased radiologic sinus CT scan severity, reduced FEV_1 levels, and significantly greater systemic corticosteroid utilization. These findings are consistent with the notion of a unified airway hypothesis according to which upper airway inflammation contributes to lower airway disease and vice versa.[9]

Patients experiencing frequent episodes of AECRS were also more likely to have nasal polyposis as compared with patients experiencing infrequent episodes of AECRS in this study. Although treatment recommendations for CRS with nasal polyps (CRSwNP) place less emphasis on antibiotic use as compared with the treatment recommendations for CRS without nasal polyps, a previous study has shown a benefit with doxycycline in patients with CRSwNP in shrinking polyp size, which may explain our finding of higher prevalence of nasal polyposis in the frequent exacerbation group.[10] Additionally, nasal polyps often recur after sinus surgery, which could lead to patients with CRSwNP being a high-risk population for frequent exacerbations.[11] Sinus surgery was also associated with frequent episodes of AECRS, which is an expected finding, as recurrent infections and severe disease are clinical characteristics that often lead to considering surgical options. Our study also showed a female predominance in both the frequent and infrequent exacerbation groups, which supports previous literature in which women were found to be more likely to have CRS without nasal polyps and CRS in general.[12-14] Higher BMI was associated with frequent episodes of AECRS, as in previous literature on CRS[15] and similar to the association between obesity and exacerbation-prone asthma (defined as ≥3 exacerbations per year).[16] The absolute difference in BMI in our study was minimal, however, so the clinical significance of this finding is unclear.

Limited literature has previously focused on an at-risk phenotype for frequent acute exacerbations with utilization of antibiotics within the entire population of patients with CRS.[12,17] Recent studies have found associations between acute exacerbations of CRS and CRS symptomatology with BMI, asthma, allergic rhinitis, and history of sinus surgery. However, these studies either relied on self-reported antibiotic use to identify acute exacerbations or did not verify a diagnosis of CRS in their cohort via objective measures.[15,18-20] This is the first study to our knowledge that showed disease associations with a phenotype of patients with CRS with frequent exacerbations that was vigorously adjudicated via chart review. Moreover, our study utilized a cutoff for frequent AECRS episodes, highlighting a potential high-utilizer phenotype, which could have significant clinical and economic implications. Our results suggest that this unique subgroup of patients with CRS has high risk for complications and could be considered for advanced therapies

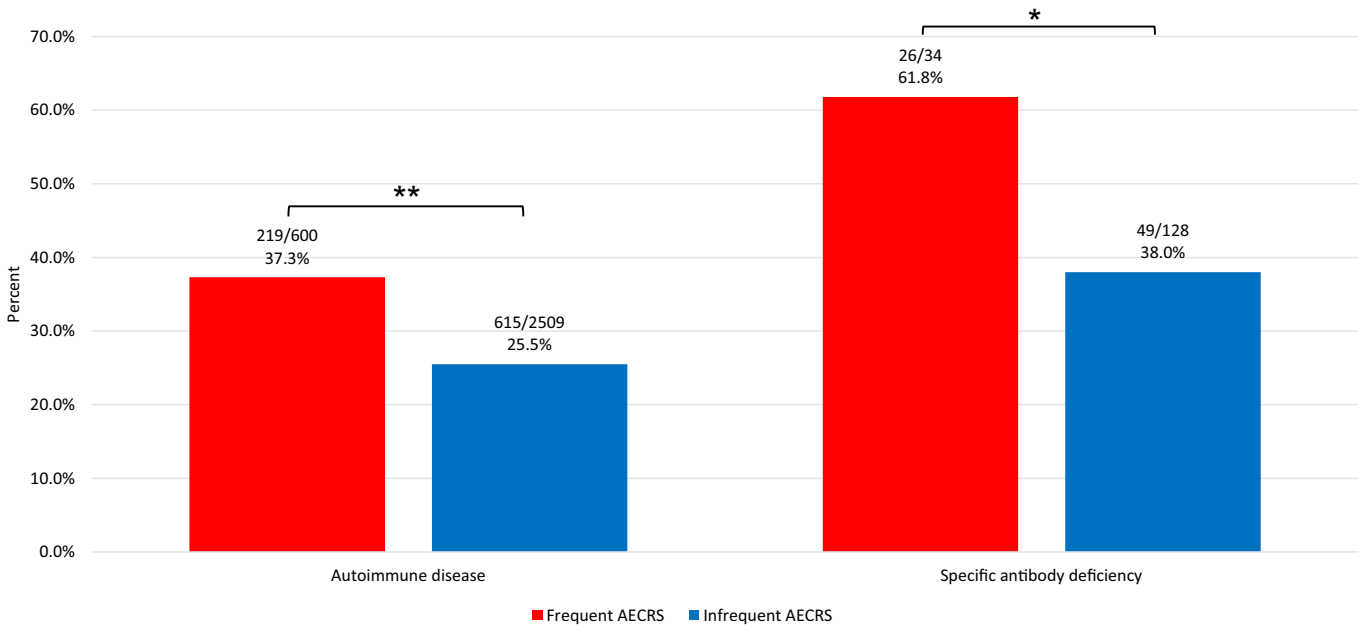

FIG 4. Autoimmune disease and specific antibody deficiency associations with frequent AECRS. *$P = .022$; **$P < .001$. P values calculated using the Pearson chi-square test.

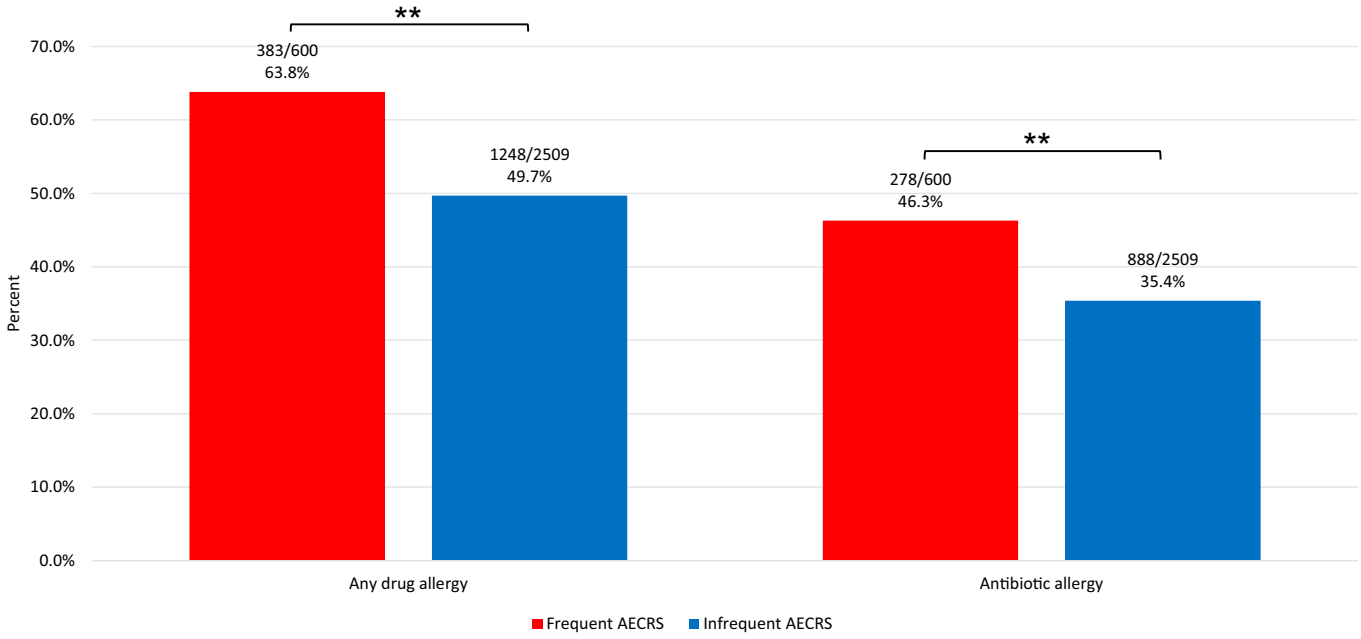

FIG 5. Antibiotic allergy and any drug allergy associations with frequent AECRS. **$P < .001$ (calculated using the Pearson chi-square test).

to reduce exacerbation frequency. Expert groups have yet to establish an appropriate cutoff for frequent episodes of AECRS, so we chose 4 episodes of AECRS per year to define a high frequency of exacerbations based on otolaryngology practice guidelines regarding recurrent acute rhinosinusitis.[2]

Rhinosinusitis has been shown to account for more antibiotic prescriptions than has any other diagnosis in the outpatient setting, highlighting the significant antibiotic exposure in patients with CRS.[21] Our study suggests the presence of a clinical phenotype of patients with CRS experiencing frequent episodes of AECRS who are at greater risk for disease-related morbidity due to antibiotic exposure, including high numbers of medication allergies. In addition, these patients are at risk for the development of antimicrobial resistance, which has public health implications. Studies have shown an association between antimicrobial-resistant organisms and patients with CRS.[22,23]

The US Centers for Disease Control and Prevention consider antibiotic resistance an important public health issue that is implicated in an estimated 23,000 deaths annually and provides incentives to investigate and improve antibiotic stewardship in CRS.[24] Recently, *Clostridium difficile* colitis has been associated with antibiotic use, and strains are appearing to become increasingly virulent.[25] In addition, we have found higher utilization of systemic corticosteroids in patients with frequent exacerbations, putting this group at even higher risk for known complications of long-term systemic corticosteroid use, such as diabetes mellitus, ophthalmologic diseases, osteoporosis, adrenal suppression, and psychiatric symptoms.

A strength of our study is the large cohort size, which enabled capture of data associated with a large number of exacerbations. Acute exacerbations were determined by antibiotic prescriptions, fortified by a chart review by the study investigators to confirm a proper sinus-related indication. This likely provides a more accurate evaluation of AECRS frequency compared with patient recall and strengthens our ability to draw associations based on the study findings. Prescriptions for oral corticosteroids were also based on EMR data rather than on patient recall, making our study a more reliable representation of oral corticosteroid use. Physician-coded diagnoses were utilized to assess clinical factors associated with AECRS, which would also remove the possibility of bias from patient recall. Asthma severity and CRS severity were based on objective tests (spirometry, pulmonary function tests, and sinus CT scans), which eliminates potential biases from utilization of nonobjective measures.

A limitation of this study is the retrospective observational study design, which limits the ability to draw causal inferences from the data. This is a single-center study at a large academic medical center with a multidisciplinary sinus center in an urban area, which promotes the scale of the study but potentially limits the generalizability of the study findings to primary care or rural patient populations. We also cannot account for patients seeking care at other nonaffiliated institutions during the study period, although we believe that this factor would bias the results toward the null hypothesis. Because we evaluated antibiotic prescription issuance only and did not confirm medication use, another possible source of bias derives from uncertain adherence. An additional potential limitation to our study is that some exacerbations captured in our data could have been viral in etiology and antibiotics could have been inappropriately prescribed. In our study we found a higher frequency of autoimmune diseases in those with frequent exacerbations; however, a limitation of this analysis is that we did not analyze for the effect of immunomodulatory drugs on the frequency of exacerbations. Similarly, because of the smaller numbers, we did not examine for differences in frequent versus infrequent exacerbations between patients with organ-specific autoimmune diseases. Our methodology for categorizing sinus severity on sinus CT scans has not been fully validated and could have introduced misclassification bias. However, because our institution is a multidisciplinary sinus center, its radiologists have significant experience reading sinus radiologic studies, thus adding to the potential accuracy of classification in this study.

Future areas of research should include a replication study, preferably with a prospective multicenter design. If a phenotype of patients with CRS who are susceptible to frequent episodes of AECRS is confirmed, the use of advanced therapies, such as biologic agents targeting type 2 inflammation or early surgical interventions could be considered in this group to reduce exacerbations. Previous studies have shown that monoclonal antibodies targeting type 2 inflammation are beneficial in treating symptoms in CRS and reducing polyp size in patients with CRSwNP.[26-30] Dupilumab recently showed a reduction in polyp size, sinus opacification, and severity of symptoms in patients with inadequately controlled CRSwNP in phase III trials, and this has led to a recent US Food and Drug Administration indication as an add-on maintenance therapy in these patients.[30] However, the question as to whether biologic agents treating type 2 inflammation would have an effect on reducing exacerbation frequency or antibiotic and/or systemic corticosteroid use still remains. A small retrospective chart review showed a reduction in antibiotic use and steroid dependence with omalizumab therapy in patients with CRS, which indicates the possibility of utilizing biologics for this indication in the future.[31] The beneficial effect of biologic agents on frequency of asthma exacerbation has certainly been well established and is encouraging in consideration of the unified airway hypothesis.[32]

In summary, we found that AECRS was common among patients with CRS, with 19.3% of patients in our clinical cohort being classified as having frequent exacerbations (ie, more than 4 exacerbations per year). We found several important clinical characteristics associated with the frequent exacerbation phenotype. In particular, compared with those with infrequent exacerbations, patients with frequent AECRS had more severe upper and lower airway disease. Altogether, our findings suggest that patients with frequent exacerbations of CRS may have a unique clinical phenotype that could help distinguish them from other patients with CRS. By identifying this higher-risk group of patients, preventive treatments could be initiated earlier in the disease course to reduce AECRS frequency, antibiotic use, and overall morbidity.

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Clinical implications: This study characterizes patients with CRS who are at high-risk for recurrent exacerbations requiring frequent courses of antibiotics and steroids and can benefit from targeted interventions to reduce exacerbation frequency.

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