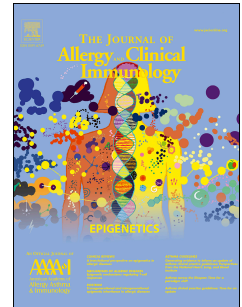


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Clinical Factors Associated with Acute Exacerbations of Chronic Rhinosinusitis

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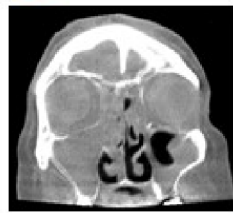
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Clinical Factors Associated with Acute Exacerbations of Chronic Rhinosinusitis



Chronic
Rhinosinusitis
(CRS)
Retrospective Cohort
N = 3109



19.3% of patients with
CRS experience
frequent exacerbations
(≥ 4 antibiotics in 1 year)

Frequent
exacerbations
associated
with



- Allergic rhinitis
- Radiographic sinus disease severity
- Nasal polyposis
- Asthma
- Lower FEV₁
- Eosinophils $\geq 150/\mu\text{L}$
- $\uparrow$ systemic corticosteroid use
- Autoimmune disease
- Antibody deficiency
- Antibiotic allergy



**High-risk CRS
Phenotypes**



Clinical Factors Associated with Acute Exacerbations of Chronic Rhinosinusitis

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Conflict of Interest Disclosure:

A.T. Peters has served as an advisor to Sanofi, AstraZeneca, Novartis, and Optinose.

R.P. Schleimer reports grants from NIH during the conduct of the study; and reports personal fees from serving as a consultant for Intersect ENT, GlaxoSmithKline, Allakos, Aurasense, Merck, BioMarck, Sanofi, AstraZeneca/Medimmune, Genentech, Exicure Inc, Otsuka Inc, Aqualung Therapeutics Corp, and ActoBio Therapeutics, outside the submitted work. In addition, R.P. Schleimer has Siglec-8 and Siglec-8 ligand related patents licensed to Allakos Inc.

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The rest of the authors declare they have no relevant conflict of interests.

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Abstract

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

Objective: The objective of this study was to identify clinical factors associated with frequent acute exacerbations of chronic rhinosinusitis (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 ≥ 4 episodes over a 12-month period in which an antibiotic was prescribed for worsening sinus symptoms and infrequent AECRS was defined as 0-3 episodes. Clinical factors including asthma, allergic rhinitis, eosinophil count ≥ 150 cells per microliter ($\geq 150/\mu\text{L}$), and autoimmune disease were evaluated for associations between the two groups.

Results: Of the 3109 CRS patients identified, 600 (19.3%) were classified as having frequent exacerbations. Asthma, allergic rhinitis, eosinophil count $\geq 150/\mu\text{L}$, and autoimmune disease were associated with frequent AECRS with statistically significant adjusted odds ratios (aOR) after controlling for age, race, and gender 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 $\geq 150/\mu\text{L}$ 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, lower FEV₁, radiographic sinus disease severity, nasal polyposis, and systemic corticosteroid use were also associated with frequent AECRS.

70

71 **Conclusion:** Patients with frequent episodes of AECRS were characterized by a higher
72 prevalence of asthma, allergic rhinitis, eosinophil count $\geq 150/\mu\text{L}$, autoimmune disease, and other
73 allergic and immunologic diseases. These findings identify a high-risk phenotype of patients
74 with CRS for preventative interventions to reduce exacerbation frequency.

75

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

79

80 **Capsule Summary:** This study identifies associations between high-risk patients with CRS
81 experiencing frequent exacerbations requiring antibiotics, and allergic and immunologic
82 diseases. Improved understanding of this patient population can lead to targeted interventions to
83 reduce exacerbation frequency.

84

85 **Key Words:** Chronic rhinosinusitis, exacerbation, antibiotics, asthma, allergic rhinitis,
86 eosinophils, autoimmune disease

87

88 **Abbreviations:**

89 CRS: Chronic rhinosinusitis

90 CT scan: Computed tomography scan

91 CRSwNP: Chronic rhinosinusitis with nasal polyps

92 CRSsNP: Chronic rhinosinusitis without nasal polyps

- 93 AECRS: Acute exacerbation of chronic rhinosinusitis
- 94 QOL: Quality of life
- 95 EMR: Electronic medical record
- 96 ICD-9: International Classification of Diseases, Ninth Revision
- 97 BMI: Body mass index
- 98 FEV₁: Forced expiratory volume in one second
- 99
- 100

INTRODUCTION

Chronic rhinosinusitis (CRS) is a chronic inflammatory condition of the nose and paranasal sinuses with clinical symptoms of rhinorrhea, nasal congestion, sinus pressure/pain, and decreased sense of smell lasting for a duration of 12 weeks or greater. The prevalence of CRS has been estimated between 6% and 12% of the US population^{1,2} and the economic burden of this disease was estimated between \$60.2 and \$64.5 billion US dollars in 2011, with a large proportion spent on office-based care and outpatient medications.³ Patients with CRS experience significant reductions in quality of life (QOL) due to their symptoms⁴ 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 exacerbations of chronic rhinosinusitis (AECRS), is unknown but is likely to be highly variable among all CRS patients. 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 CRS patients are at greatest risk for frequent exacerbations could identify a patient population that would benefit from advanced therapies to potentially reduce AECRS frequency and the associated antibiotic usage and overall morbidity. In this retrospective study, we first determined the frequency of AECRS in our clinical cohort by identifying those CRS patients who received an antibiotic prescription for worsening sinus

124 symptoms over the course of a year. We then evaluated whether certain clinical factors
125 distinguished patients with CRS experiencing frequent acute exacerbations from those who did
126 not.
127
128

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) a sinus computed tomography (CT) scan demonstrating sinomucosal inflammation at any point in their clinical history, and 3) were evaluated in either the Otolaryngology or Allergy and Immunology clinics at Northwestern University (Figure 1). CRS was diagnosed based on 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 was analyzed for patients seen between January 1, 2014 and May 30, 2016. Demographic information including age, gender, race, ethnicity (Hispanic vs non-Hispanic), body mass index (BMI), and smoking status was obtained. There were no age exclusions in this study however, being a tertiary adult care hospital, patients were 18 years or older.

An acute exacerbation of chronic rhinosinusitis 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 CRS patients with 0-3 antibiotic prescriptions for CRS were classified as having infrequent AECRS. The cutoff of 4 prescriptions was selected based on the definition of recurrent acute rhinosinusitis from expert consensus rhinosinusitis guidelines.²

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

The presence of asthma and allergic rhinitis was assessed via ICD-9 diagnosis codes 493.x and 477.x respectively. Forced expiratory volume in one second (FEV₁) percent predicted from either clinic spirometry or formal pulmonary function testing was determined from the charts during the study period and utilized to categorize patients' asthma as either mild (>80 percent predicted), moderate (60-80 percent predicted), or severe (<60 percent predicted) based on 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 categorical variable using ≥ 150 cells per microliter ($\geq 150/\mu\text{L}$) as a cutoff for analysis.

Identification of CRS phenotypes and severity

Sinus CT scans completed at any point in the 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. While 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. 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 two groups.

Identification of autoimmune disease and antibody deficiency

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

Identification of drug allergy

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

Study endpoints

The present study examined associations between frequent AECRS episodes and the following factors: asthma, allergic rhinitis, eosinophil count $\geq 150/\mu\text{L}$, autoimmune disease, age, gender, race, ethnicity, smoking status (current, former, never), BMI, any drug allergy, antibiotic allergy, nasal polyposis, sinus surgery, sinus CT scan severity, total systemic corticosteroid prescriptions, any systemic corticosteroid prescription, FEV₁ percent predicted, asthma severity based on FEV₁ percent predicted, hypogammaglobulinemia, specific antibody deficiency, and total IgE. Of these factors, asthma, allergic rhinitis, eosinophil count $\geq 150/\mu\text{L}$, and autoimmune disease were variables of particular interest, therefore logistic regression analysis was performed to control for age, race, and gender as potential confounders.

Statistical analysis

Pearson's chi-squared test of independence was used for comparisons between the different patient groups regarding asthma, allergic rhinitis, eosinophil count $\geq 150/\mu\text{L}$, sinus CT scan severity, any systemic corticosteroid prescription, sinus surgery, nasal polyposis, asthma severity based on FEV₁ percent predicted, autoimmune disease, hypogammaglobulinemia, antibody deficiency, antibiotic allergy, drug allergy, gender, race, ethnicity, and tobacco use. 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 two patient groups and absolute eosinophil counts.

Student's two-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 $\geq 150/\mu\text{L}$, and autoimmune disease, after controlling for age, race, and gender. A P value of less than 0.05 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

Using our algorithm, 3109 patients with CRS were evaluated between January 1, 2014 and May 31, 2016 at our tertiary care institution (Figure 1). Of these 3109 patients, 600 were classified as having frequent episodes of AECRS (19.3%) and 2509 with infrequent episodes of AECRS (80.7%) (Figure 1). There was no statistically significant difference in age between the two groups, each with a mean age of approximately 50 years (Table I). Fifty-eight percent of the cohort was female, and there was a significant association between female gender and frequent AECRS ($p=0.012$). The majority of the cohort was white patients, but there was an association between non-white race and the frequent AECRS group. While 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 ($p=0.03$).

Asthma, allergic rhinitis, and eosinophil count ≥ 150 cells per microliter

Asthma, allergic rhinitis, and eosinophil count $\geq 150/\mu\text{L}$ were each associated with frequent episodes of AECRS (Figure 2). Patients with frequent episodes of AECRS also had greater asthma severity as determined by FEV₁ percent predicted values (Figure 5). Specifically, when analyzing severe asthma as a separate variable, severe asthma was associated with frequent episodes of AECRS. Asthma, allergic rhinitis, and eosinophil count $\geq 150/\mu\text{L}$ maintained an association with frequent episodes of AECRS after controlling for age, race, and gender (Table II). When analyzing absolute eosinophil counts as a continuous variable, higher absolute eosinophil counts showed an association with frequent AECRS (aOR 1.32 95%, CI 1.15-1.52, $p<0.001$; $n = 2275$). Total IgE levels were not statistically different between the two groups

([Median Interquartile Range] Frequent: 77.8 kU/L [19.40 - 327.00] vs Infrequent: 113.00 kU/L [25.50 - 399.00]; $P = 0.414$; $n = 192$).

CRS phenotype and severity

Patients with frequent episodes of AECRS had greater sinus disease severity as determined by sinus CT scans (Figure 5). 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 to the infrequent group (3.91 ± 4.51 vs 1.07 ± 1.85 , $P < 0.001$). Patients with frequent episodes of AECRS were more likely to have nasal polyposis (Figure 2) and a prior history of sinus surgery (Frequent, 266 patients (44.3%) vs Infrequent, 813 patients (32.4%); $P < 0.001$).

Autoimmune disease and antibody deficiencies

Autoimmune disease and specific antibody deficiency were associated with frequent episodes of AECRS (Figure 3). Autoimmune disease maintained an association with frequent episodes of AECRS after controlling for age, race, and gender (Table II). There was a trend towards higher prevalence of hypogammaglobulinemia in the group with frequent AECRS, however this was not statistically significant (Frequent, 53/305 patients (17.4%) vs Infrequent, 84/646 patients (13.0%); $P = 0.085$).

Drug allergy

Any drug allergy or antibiotic allergy was more frequently reported by patients with frequent AECRS vs infrequent AECRS (Figure 4).

DISCUSSION

This large cohort study found that patients with frequent episodes of AECRS were significantly more likely to have asthma, allergic rhinitis, eosinophil count $\geq 150/\mu\text{L}$, autoimmune disease, and specific antibody deficiency as compared to patients with infrequent episodes of AECRS. This study also found that patients with frequent episodes of AECRS had greater upper and lower airway disease severity as determined by increased radiologic sinus CT scan severity, reduced FEV₁ levels, and significantly greater systemic corticosteroid utilization as compared to patients experiencing infrequent episodes of AECRS. These findings are consistent with the notion of a unified airway hypothesis where 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 to patients experiencing infrequent episodes of AECRS in this study. While treatment recommendations for CRSwNP place less emphasis on antibiotic use as compared to CRSsNP, a previous study has shown a benefit with doxycycline in CRSwNP in shrinking polyp size and that 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 which often lead to considering surgical options. Our study also showed a female predominance in both frequent and infrequent exacerbation groups, which supports previous literature in which women were found to be more likely to have CRSsNP and CRS in general.¹²⁻¹⁴ Higher BMI was

associated with frequent episodes of AECRS, similar to previous literature in CRS¹⁵ and similar to the association between obesity and exacerbation prone asthma (defined as 3 or more 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 previously has focused on an at-risk phenotype for frequent acute exacerbations utilizing 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 sinus surgery history. However, these studies have either relied upon 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 showing 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 to reduce exacerbation frequency. Expert groups have yet to establish an appropriate cutoff for frequent episodes of AECRS, so we chose 4 AECRS episodes 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 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 that 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 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 is 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 enables 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 to 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 patient recall, making it 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, sinus CT scans) which eliminates potential biases from utilizing non-objective measures.

A limitation of this study is the retrospective observational study design that limits the ability to draw causal inferences from the data. This is a single center study at a large academic medical center with a multi-disciplinary 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 non-affiliated institutions during the study period, although we believe this factor would bias the results towards the null hypothesis. Since we evaluated antibiotic prescriptions 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, due to smaller numbers we did not examine for differences in frequent vs 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 being a multidisciplinary sinus center, radiologists at this institution have significant experience reading sinus radiologic studies adding to the potential accuracy of classification in this study.

Future areas of research should include a replication study, preferably with a prospective multi-center design. If a phenotype of CRS patients 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 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 FDA indication as an add-on maintenance therapy in these patients.³⁰ The question however still remains as to whether biologic agents treating type 2 inflammation would have an effect on reducing exacerbation frequency or antibiotic and/or systemic corticosteroid use. A small retrospective chart review showed a reduction in antibiotic usage 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 asthma exacerbation frequency 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% in our clinical cohort being classified as having frequent exacerbations, i.e. more than four exacerbations per year. We found several important clinical characteristics associated with the frequent exacerbation phenotype. In particular, compared to 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 CRS patients. By identifying this higher risk group of patients, preventive treatments could be initiated earlier in the disease course to reduce AECRS frequency, antibiotic usage, and overall morbidity.

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Table I. – Clinical Characteristics

	Frequent Exacerbation Group (n=600)	Infrequent Exacerbation Group (n=2509)	p-value
Age ($\pm$ SEM)	50.0 $\pm$ 15.0	49.0 $\pm$ 15.6	0.178
Sex, no. (%)			
Male	220 (36.7)	1063 (42.4)	0.012
Female	380 (63.3)	1446 (57.6)	
Race, no. (%)			
White	343 (63.6)	1471 (69.6)	0.011
Black	57 (10.6)	221 (10.4)	
Other	139 (25.8)	423 (20.0)	
Hispanic, no. (%)	38 (7.0)	145 (6.9)	0.985
BMI ($\pm$ SEM)	28.3 $\pm$ 6.6	27.6 $\pm$ 7.2	0.030
Smoking, no. (%)			
Current	24 (4.0)	109 (4.4)	0.883
Former	164 (27.3)	666 (26.6)	
Never	412 (68.7)	1729 (69.0)	

Table II. – Multivariable logistic regression analysis for primary outcome variables after controlling for age, race, and gender.

	Odds Ratio	95% Confidence Interval
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

Figure Legends

Figure 1 – Algorithm for selecting patients with frequent versus infrequent AECRS.

Figure 2 – Clinical Associations between asthma, allergic rhinitis, eosinophil count ≥ 150 cells per microliter ($\geq 150/\mu\text{L}$), and nasal polyps with frequent acute exacerbations of chronic rhinosinusitis. *P = 0.018 and **P < 0.001 by Pearson's Chi Squared test.

Figure 3 – Autoimmune disease and specific antibody deficiency associations with frequent acute exacerbations of chronic rhinosinusitis. *P = 0.022 and **P < 0.001 by Pearson's Chi Squared test.

Figure 4 – Antibiotic allergy and any drug allergy associations with frequent acute exacerbations of chronic rhinosinusitis. **P < 0.001 by Pearson's Chi Squared test.

Figure 5 – Upper and lower airway disease severity associations with frequent acute exacerbations of chronic rhinosinusitis. **P < 0.001 by Pearson's Chi Squared test.

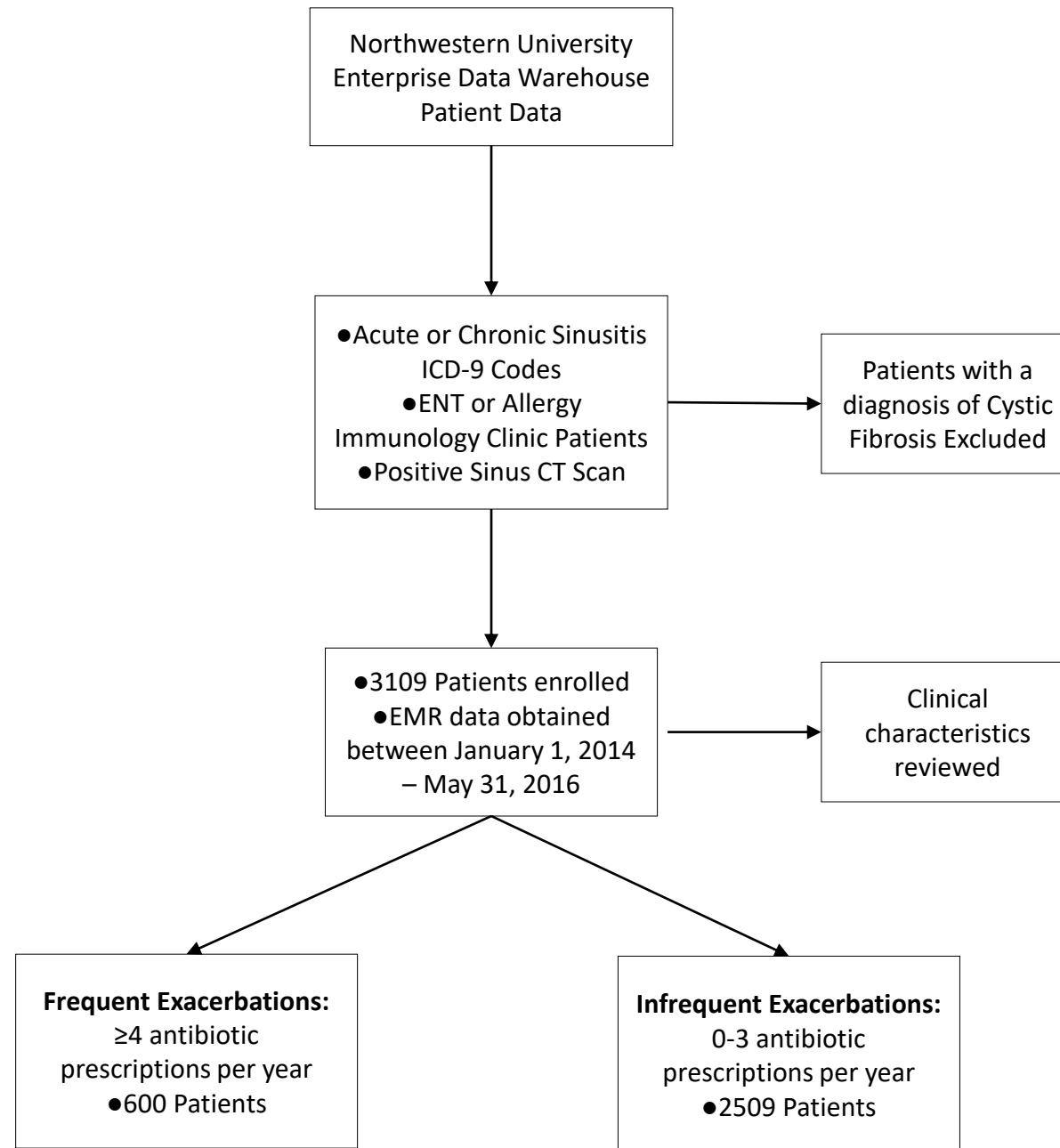


Figure 1

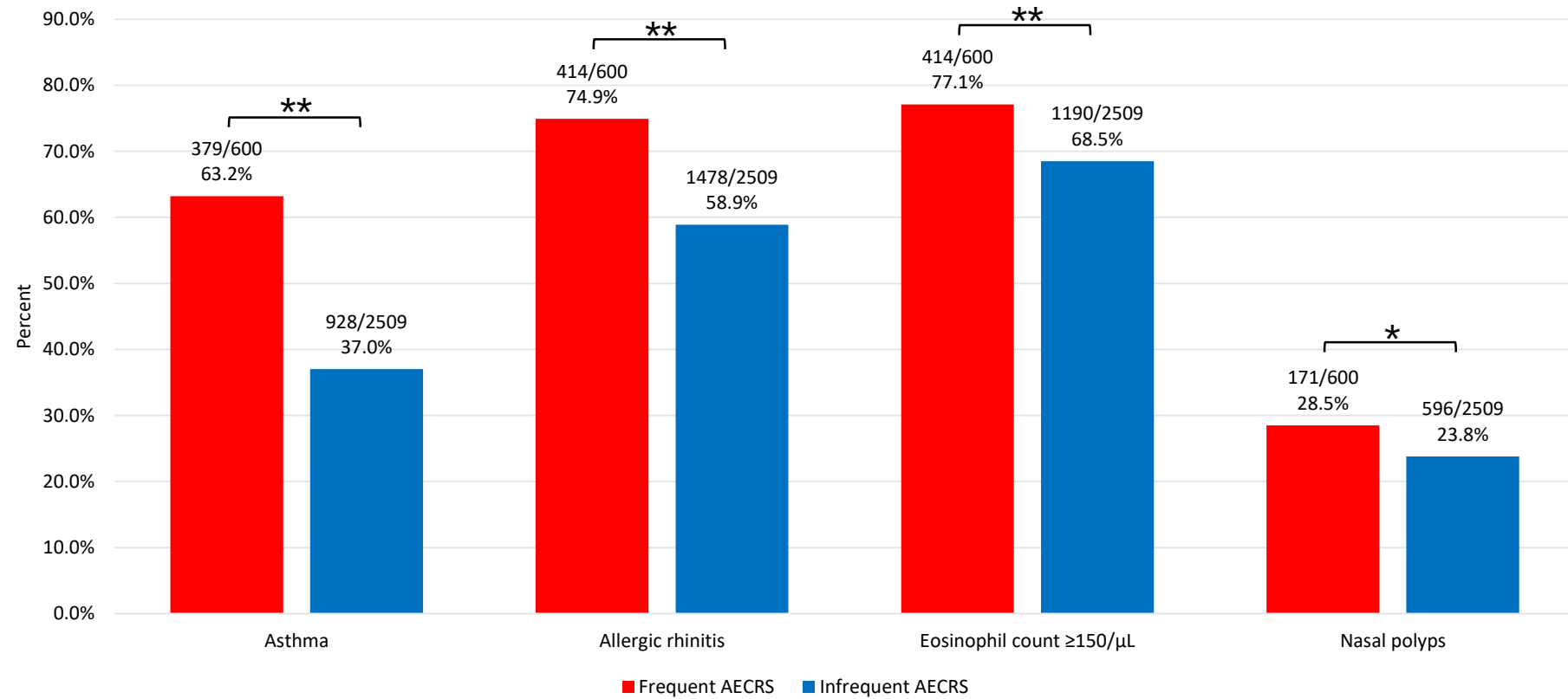


Figure 2

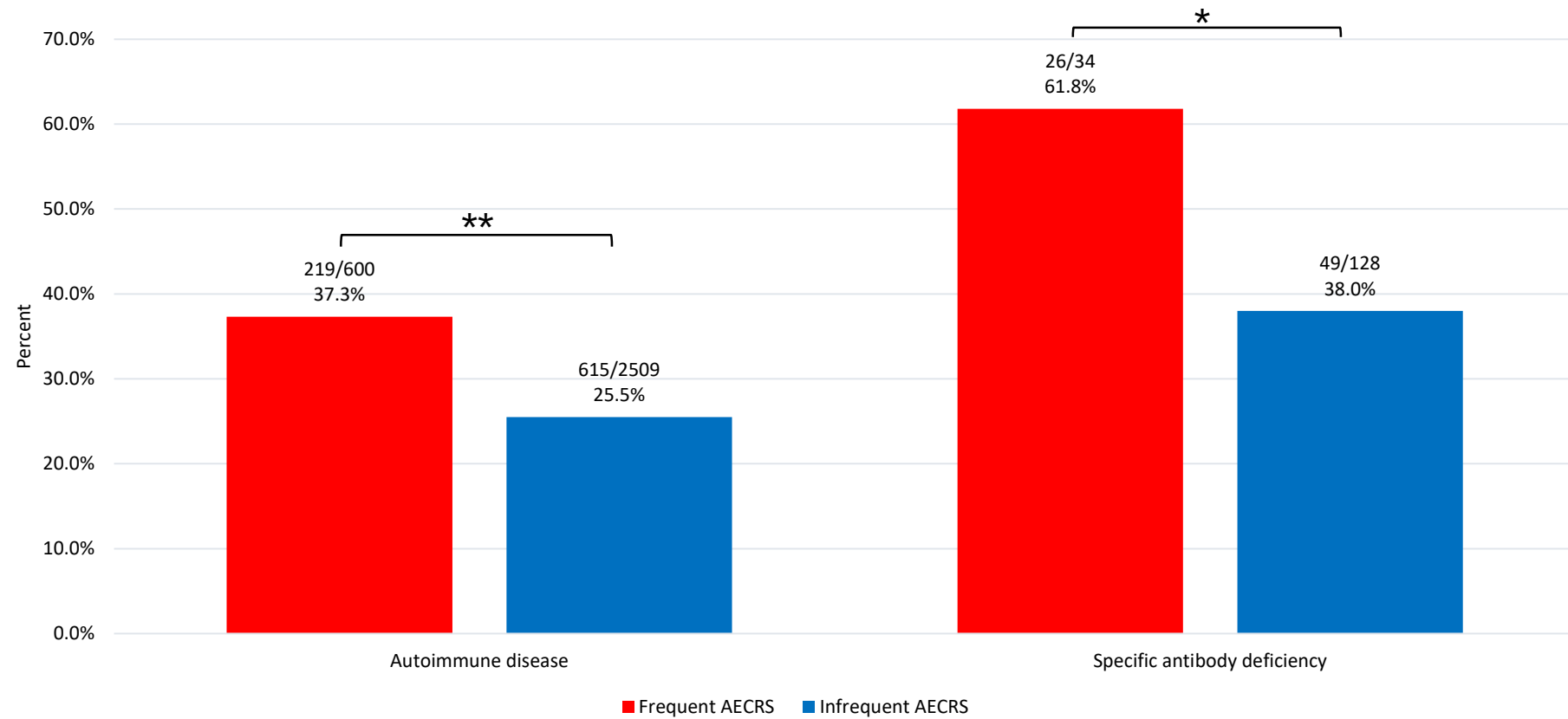


Figure 3

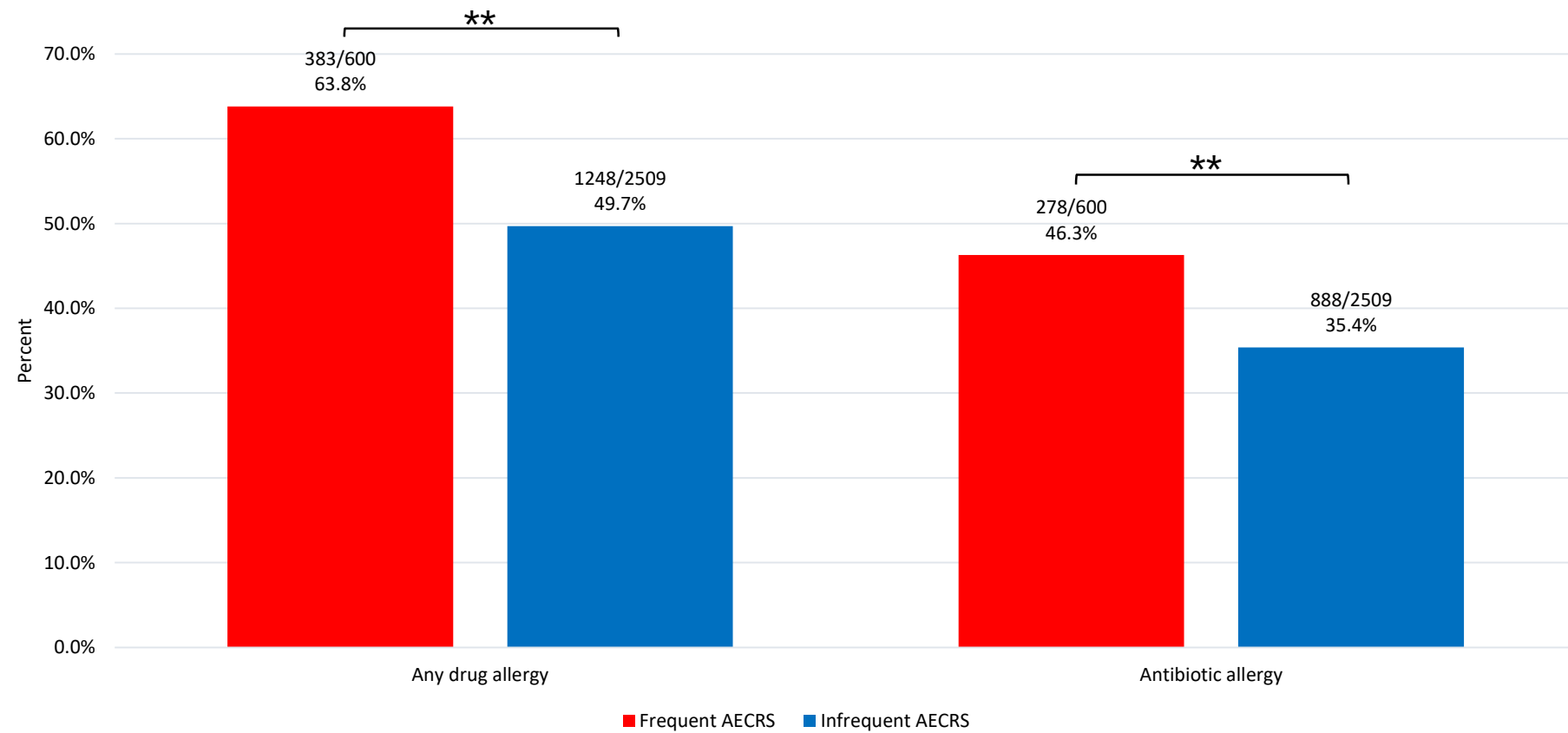


Figure 4

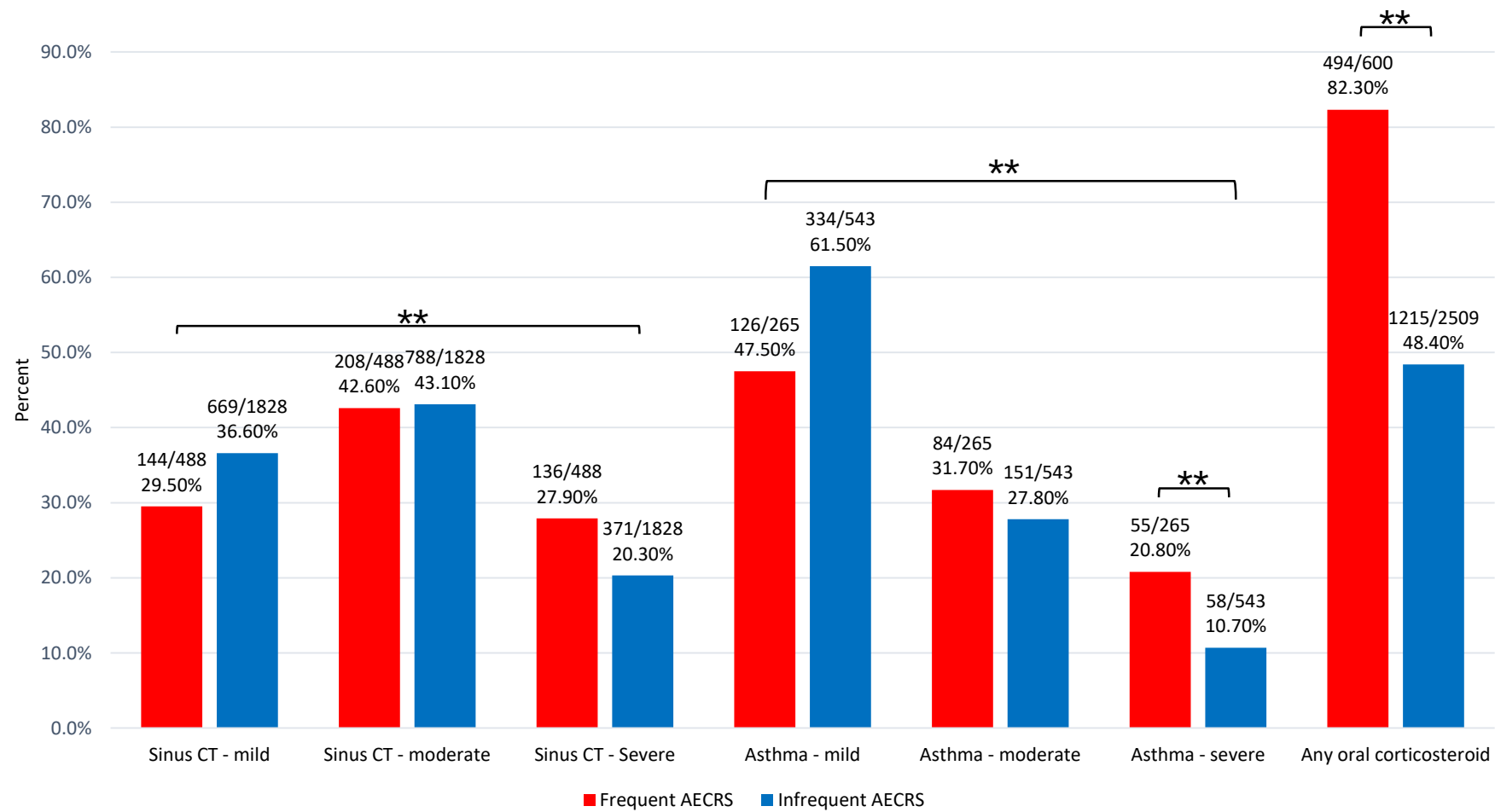


Figure 5