

# Acute Exacerbations Mediate Quality of Life Impairment in Chronic Rhinosinusitis



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**What is already known about this topic?** Antibiotic usage for chronic rhinosinusitis (CRS) is common, most often in the setting of acute exacerbations and superimposed acute rhinosinusitis. Greater antibiotic usage reflects poorer control of CRS.

**What does this article add to our knowledge?** This article establishes a link between CRS symptomatology and the need for sinusitis-related antibiotic usage. This article also shows that the need for antibiotics mediates the association between the nature of a patient's CRS, reflected by CRS symptomatology, and quality of life detriment in CRS. This mediation effect is shown to reflect the impact of acute exacerbations of CRS to decrease quality of life.

**How does this study impact current management guidelines?** This study demonstrates that acute exacerbations, for example from superimposed acute sinus infections, may be one aspect of CRS distinct from baseline symptomatology that can be targeted to improve patient quality of life.

**BACKGROUND:** Antibiotic usage in chronic rhinosinusitis (CRS) reflects poor disease control and may indicate the need for sinus surgery.

**OBJECTIVES:** The objective of this study was to (1) determine the association between CRS symptomatology, which reflects CRS pathophysiology, and sinusitis-related antibiotic usage, and (2) to determine the impact of antibiotic usage on quality of life (QOL).

**METHODS:** A prospective cross-sectional study enrolling 85 participants meeting consensus guideline criteria for CRS was conducted. Symptomatology was assessed using the 22-Item Sinonasal Outcomes Test (SNOT-22) and general health-related QOL was assessed using the EuroQol 5-dimensional visual analog scale (EQ5D-VAS). Association was sought between SNOT-22, the number of prescribed antibiotics for sinusitis in the past year, sinus infections in the past year, and EQ5D-VAS. Antibiotic usage and number of sinus infections were checked for mediation in the association between SNOT-22 and EQ5D-VAS.

**RESULTS:** The SNOT-22 score is associated with the number of antibiotics taken in the past year (relative risk = 1.02, 95% confidence interval [CI]: 1.01-1.03,  $P = .002$ ) and EQ5D-VAS ( $\beta = -0.37$ , 95% CI:  $-0.52$  to  $-0.22$ ,  $P < .001$ ). Having taken more than 2 antibiotics for sinusitis in the past year mediated 31% of the effect of SNOT-22 on EQ5D-VAS, through a mediation effect ( $P = .008$ ). Antibiotic usage highly correlated with the number of reported sinus infections ( $\rho = 0.69$ , 95% CI: 0.54-0.80,  $P < .001$ ), which also showed a similar statistically significant mediation effect between SNOT-22 and EQ5D-VAS. **CONCLUSIONS:** Sinusitis-related antibiotic usage, likely reflecting the frequency of acute CRS exacerbations, mediates the association between CRS symptomatology and QOL. Reducing the frequency of acute exacerbations may significantly enhance QOL of CRS sufferers independent of baseline symptomatology. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:422-6)

**Key words:** Acute exacerbations; Acute rhinosinusitis; Antibiotics; Chronic rhinosinusitis; EQ-5D; Quality of life; SNOT-22; Symptomatology

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Chronic rhinosinusitis (CRS) is an inflammatory disease of the sinonasal mucosa that is characterized by symptoms of nasal obstruction, mucopurulent drainage, facial pain/pressure, and hyposmia.<sup>1,2</sup> CRS is a common disease, affecting 2% to 5% of the population, and it imparts a significant quality of life (QOL) detriment.<sup>3-5</sup> The effects of CRS have been characterized from the standpoint of sinonasal symptoms as well as general health-related QOL impairments,<sup>6,7</sup> both of which are associated with physician visits, medication usage, loss of productivity, and annual health care costs on the order of 10 billion dollars.<sup>8</sup>

The difficulty and expense in treating CRS in part arises from a lack of understanding the underlying pathophysiology of this

#### Abbreviations used

CRS- Chronic rhinosinusitis  
EQ5D-VAS- EuroQol 5-dimensional survey visual analog scale  
QOL- Quality of life  
RR- Relative risk  
SD- Standard deviation  
SNOT-22- 22-Item Sinonasal Outcomes Test

disease. It is unlikely that there is one common pathway for the development of CRS. Instead, CRS is increasingly recognized as a heterogeneous disease, driven by factors such as atopy, immune dysfunction, microbes, and impaired mucociliary clearance,<sup>9-15</sup> which all converge on the final clinical phenotype defined by consensus guideline criteria for the diagnosis of CRS. It is therefore likely that the varied pathophysiologic processes underlying CRS may differentially impact the disease course and the ultimate QOL deficit imparted to patients. One large issue related to the care of patients with CRS is with respect to the use of antibiotics. Because CRS is increasingly recognized as an inflammatory, rather than just microbial, disorder, the necessity of antibiotics in the long-term management and control of CRS is a point of debate.<sup>16</sup> Moreover, disruption of the normal sinonasal microbiome, which may occur from antibiotic use,<sup>17</sup> is associated with sub-optimal outcomes in patients with CRS as well.<sup>18</sup> Nevertheless, millions of antibiotics are prescribed for CRS every year, often for acute CRS exacerbations.<sup>19</sup> Antibiotic utilization is therefore used clinically as a measure for disease control, and the frequency of acute exacerbations is often used as an indicator of the need for more aggressive treatment, including endoscopic sinus surgery.<sup>20,21</sup>

Despite the common use of antibiotics for patients with CRS, no studies have examined why patients with CRS need these antibiotics and how antibiotic usage impacts their disease course. As a first step toward studying this problem, we hypothesized that the nature of each patient's CRS, which is reflected in each patient's complex of symptoms,<sup>22</sup> would be associated with the need for (and use of) antibiotics. A prospective study of this hypothesis was our primary objective, and our secondary objective was to understand how antibiotic usage may affect QOL in patients with CRS.

## METHODS

### Study participants

This study was approved by the Massachusetts Eye and Ear Infirmary Human Studies Committee. Adult patients (18 years or older) with CRS were recruited prospectively and provided informed consent for inclusion into this cross-sectional study. All participants met consensus guideline established criteria for CRS.<sup>1,2</sup> Exclusion criteria included: (1) comorbid vasculitis, (2) comorbid cystic fibrosis, (3) comorbid sarcoidosis, and (4) the need for antibiotics for sinusitis at the time of recruitment.

### Study design and data collection

This study was designed and powered as a prospective cross-sectional study to understand the relationship between a score on the 22-Item Sinonasal Outcomes Test (SNOT-22) that is representative of the baseline of a patient with CRS and his or her prescription antibiotic usage. A total of 85 participants were enrolled to power identification of an association of medium effect (defined as  $r = 0.3$ )<sup>23</sup> between the SNOT-22 score and the number of

prescribed antibiotics courses taken in the previous year for sinusitis at a significance level of 0.05 and a power of 0.80. Data collected directly from all participants included CRS-related symptomatology as measured by the validated SNOT-22 survey,<sup>24</sup> general health-related QOL as measured by the validated EuroQol 5-dimensional visual analog scale (EQ5D-VAS) given with the 5-level EQ5D questionnaire,<sup>25</sup> age, gender, whether the participant had previous sinus surgery, whether the participant was currently using an intranasal corticosteroid medication, the number of prescribed antibiotic courses for sinusitis that were taken in the previous 1-year period (participants were asked: "How many prescribed courses of antibiotics have you taken in the last year for your sinuses or sinus infections?"), and the number of sinus infections in the previous 1-year period (participants were asked: "How many sinus infections have you had in the last year?"). Data collected from the evaluating physician included whether the patient had a history of (1) aeroallergen hypersensitivity based on formal skin or serological allergy testing, (2) asthma based on a previous diagnosis that was confirmed by clinical history, and (3) nasal polyps.

### Statistical analysis

All analysis was performed using the statistical software package R ([www.r-project.org](http://www.r-project.org), R Core Team, Vienna, Austria). When correlations were performed, a Spearman correlation was used. Univariate and multivariable associations between the SNOT-22 score (as the independent variable) and the number of prescribed antibiotics courses taken for sinusitis in the previous year (as the dependent variable) were calculated using a negative binomial regression model. Associations between SNOT-22 and antibiotics usage (as the independent variables) and EQ5D-VAS (as the dependent variable) were sought using linear regression. The effects of antibiotic usage and the number of sinus infections in the last year as possible mediators in the association between the SNOT-22 score (independent variable) and the EQ5D-VAS score (dependent variable) were determined using Sobel's indirect test for mediation<sup>26</sup> implemented by the `proximal.med()` function of the `QuantPsyc` package<sup>27</sup> and bootstrapping over our dataset with 1000 iterations.

## RESULTS

### Study participants

A total of 85 patients, 52.9% males and 47.1% females, with CRS were recruited with a mean age of 52.3 years (standard deviation [SD] = 15.6 years). Of these study participants, 30.6% were present or former cigarette smokers, 29.4% had comorbid asthma, 51.8% had at least one aeroallergen hypersensitivity, 41.2% had nasal polyps, 37.6% had a history of at least one previous sinus surgery, and 64.7% reported the current use of an intranasal corticosteroid medication. The mean SNOT-22 score, reflecting CRS symptoms severity, was 36.8 (SD = 23.2). Over the previous year, study participants had taken a mean of 1.5 (SD = 1.9) and median of 1.0 (interquartile range = 2.0) courses of antibiotics for sinusitis. Although only patients with a suggestive clinical history were tested as a part of routine evaluation, only 1 patient in our cohort was found to have an immunodeficiency that was deemed to be a mild IgA and IgG subclass deficiency.

### SNOT-22 score is associated with CRS-associated antibiotic usage

We first sought a relationship between the number of prescribed antibiotic courses that each participant completed in the

previous year and the SNOT-22 score (Figure 1). We found a statistically significant correlation ( $\rho = 0.46$ ,  $P < .001$ ) between the number of prescribed antibiotics each participant completed in the previous year and the SNOT-22 score. We next sought to determine whether the SNOT-22 score, as a reflection of CRS severity, was associated with CRS-associated antibiotic usage in the previous year and found a statistically significant association (relative risk [RR] = 1.02, 95% CI: 1.01-1.04,  $P < .001$ ). This association between SNOT-22 remained statistically significant (RR = 1.02, 95% CI: 1.01-1.03,  $P = .002$ ) even after controlling for age, gender, comorbid asthma, nasal polyps, comorbid aeroallergen hypersensitivity, and intranasal corticosteroid usage. Because an RR of 1.02 for antibiotic usage associated with every 1-point increase in the SNOT-22 score may be hard to interpret from the standpoint of clinical significance, this result can also be thought of as corresponding to a 2-fold RR for antibiotic usage with every 30-point increase in the SNOT-22 score.

### Antibiotic usage mediates the association between SNOT-22 and general health-related QOL detriment in patients with CRS

It has been well described that CRS is associated with decreased general health-related QOL. We next sought to understand if increased antibiotic usage contributed to this decrease in QOL. We first found that SNOT-22 was negatively associated with general health-related QOL as reflected by the EQ5D-VAS ( $\beta = -0.37$ , 95% CI:  $-0.52$  to  $-0.22$ ,  $P < .001$ ). Similarly, using more than 2 courses of antibiotics for sinusitis in the previous year was negatively associated with EQ5D-VAS ( $\beta = -19.44$ , 95% CI:  $-27.46$  to  $-11.42$ ,  $P < .001$ ). We next sought evidence of mediation by antibiotic usage in the association between SNOT-22 and EQ5D-VAS. When a variable is said to mediate the effect between an independent variable and a dependent variable, this implies that some or all of the effect of the independent variable on the dependent variable goes through the mediating variable. In this case, we asked whether the effect of SNOT-22 on EQ5D-VAS was the indirect result of an association between SNOT-22 and antibiotic use followed by an association between antibiotic use and EQ5D-VAS (Figure 2). We found a statistically significant mediation effect (effect size =  $-0.11$ , 95% CI:  $-0.23$  to  $-0.03$ ,  $P = .008$ ) for having used more than 2 courses of antibiotics for sinusitis in the previous 1-year period that accounted for 31% of the total effect of SNOT-22 on EQ5D-VAS.

### The impact of antibiotic usage in patients with CRS likely reflects superimposed acute rhinosinusitis or CRS flares

We next sought to better understand the clinical correlate for antibiotic use in CRS, which we have now found to partially mediate the association between SNOT-22 and EQ5D-VAS. We additionally asked each participant how many sinus infections he or she had in the previous 1 year so we investigated whether antibiotic use correlated with acute on CRS, as a reflection of acute CRS exacerbations. We found that the reported number of sinus infections and the reported number of antibiotic courses taken in the previous year were highly correlated (Figure 3) ( $\rho = 0.69$ , 95% CI: 0.54-0.80,  $P < .001$ ) and higher SNOT-22 score also was associated with the patient reporting a sinus infection (RR = 1.03, 95% CI: 1.01-1.04,  $P <$

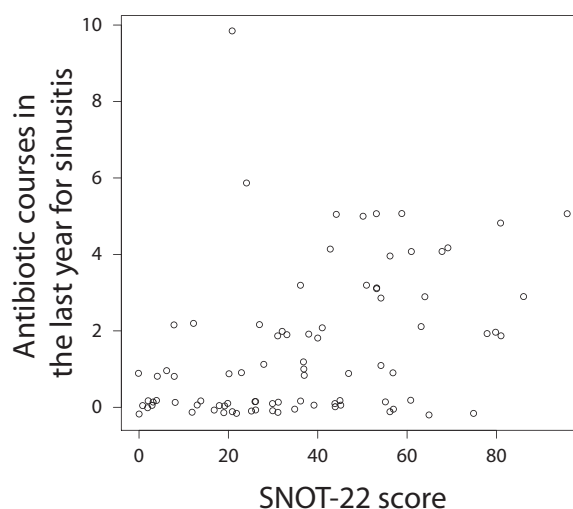


**FIGURE 1.** A plot showing the reported number of antibiotics prescribed for sinusitis in the last year vs baseline SNOT-22 score. SNOT-22, 22-Item Sinonasal Outcomes Test.

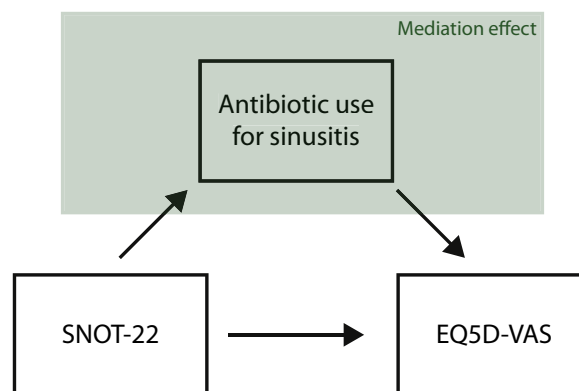


**FIGURE 2.** Conceptual framework for mediation by antibiotic usage in the association of SNOT-22 with EQ5D-VAS. EQ5D-VAS, EuroQol 5-dimensional visual analog scale; SNOT-22, 22-Item Sinonasal Outcomes Test.

.001), after adjusting for age, gender, aeroallergen sensitization, polyps, asthma, and intranasal corticosteroid use. Likewise, similar to the number of antibiotics taken for sinusitis, the number of sinus infections reported by the participant in the last year was negatively associated with general health-related QOL as reflected by the EQ5D-VAS ( $\beta = -16.30$ , 95% CI:  $-24.89$  to  $-7.72$ ,  $P < .001$ ). We also found a statistically significant mediation effect for more than 2 sinus infections in the preceding year between SNOT-22 and EQ5D-VAS (effect size =  $-0.11$ , 95% CI:  $-0.24$  to  $-0.01$ ,  $P = .026$ ) that accounted for 35% of the total effect of SNOT-22 on EQ5D-VAS.

### DISCUSSION

CRS is a common disease that leads to a significant QOL detriment as well as billions of dollars of health care expenditure every year. Costs attributable to CRS include not only those

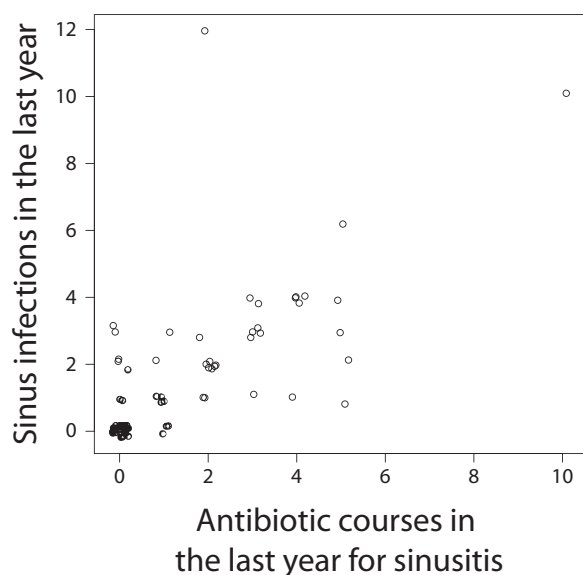


**FIGURE 3.** A plot showing the reported number of sinus infections in the last year and the number of antibiotics prescribed for sinusitis in the last year.

related to lost productivity but also direct costs from frequent physician visits and prescription medication usage.<sup>8</sup> Historically, antibiotics have been used in efforts to eradicate CRS, but our increasing understanding of the inflammatory, rather than infectious, nature of the disease has called into question the utilization of antibiotics as curative agents.<sup>16</sup> Previous studies have shown that antibiotics, including macrolide antibiotics that may have additional anti-inflammatory properties, lead to improved sinonasal symptomatology during treatment that may be sustained in the short term<sup>28-31</sup> but not in the long term.<sup>32</sup> In addition, although antibiotics may lead to short-term improvement of sinonasal symptomatology, side effects such as allergic reactions, rashes, gastrointestinal distress, and *Clostridium difficile* colitis may occur. Thus outside of continuous, long-term use of macrolides, antibiotics in the setting of treatment for CRS are typically utilized for acute exacerbations. Frequent usage of antibiotics for acute exacerbations reflects poorer CRS control and may also serve as an indication for more aggressive treatment of CRS, including endoscopic sinus surgery.<sup>2,20,21</sup> In this study, we study antibiotic use in patients with CRS and show for the first time that antibiotic use, reflecting acute exacerbations of CRS, causes a significant QOL detriment that is separate from the chronic sinonasal symptomatology that has long been considered as the source of QOL detriment in CRS.

There is a trend toward limiting antibiotic usage for CRS to reduce drug resistance and the side effects associated with antibiotics. At present, the most accepted usage of antibiotics in the setting of CRS is for acute exacerbations, such as from superimposed acute sinus infections, on top of the baseline sinonasal symptomatology of CRS.<sup>2</sup> Despite this trend, patients with CRS are spending, on average, hundreds of dollars every year on prescription antibiotics.<sup>5,20,21</sup> To reduce antibiotic usage in patients with CRS, we must first begin to understand why antibiotics are prescribed for these patients. To date, there have been no studies that have prospectively studied why patients with CRS may require antibiotics. As a first step toward better

understanding antibiotic usage for CRS, we have hypothesized that the nature of each patient's CRS may directly impact the need for antibiotics. Previous work has shown that CRS symptomatology, as reflected by the SNOT-22 score, may reflect different underlying pathophysiologic processes that manifest through the presence of predominant and unique subsets of symptoms.<sup>22</sup> We have therefore hypothesized that the baseline symptomatology of patients with CRS would be associated with antibiotic usage.

Here we have shown that the SNOT-22 score of patients with CRS is correlated and associated with the number of prescribed antibiotics that these patients have taken in the last year for sinusitis. Moreover, we have found that this association possibly reflects a more fundamental aspect of how CRS diminishes QOL. Previous work has reported that CRS may lead to decreased general health-related QOL through its associated symptomatology.<sup>33</sup> However, there has been no previous study that has sought to identify the contribution of acute exacerbations to decreased QOL in patients with CRS. Our findings now show that the frequency of acute exacerbations may be one mechanism for reducing QOL that is distinct from baseline CRS symptomatology. Validated tools for assessing disease-specific and general health-related QOL in CRS, such as the SNOT-22 and EQ5D, respectively, do not reflect the frequency of acute exacerbations so this aspect of CRS is often overlooked. Here we have made the novel finding that in patients with CRS, the use of more than 2 sinusitis-related antibiotic courses in the previous year is negatively associated with general health-related QOL and that this antibiotic usage may account for more than 30% of the association between CRS symptoms and the general health-related QOL through a mediation effect. We have additionally characterized this novel finding by showing that the impact of antibiotic usage on the QOL detriment in patients with CRS is likely related to acute exacerbations (eg, acute rhinosinusitis superimposed on the baseline chronic sinonasal symptomatology of CRS) due to the strong correlation with the patient-reported frequency of sinus infections.

These findings have several important implications. First, we provide the first direct evidence that the nature of the patient's disease, as reflected by CRS symptomatology, is associated with the need for antibiotic usage and that this association is likely due to the severity and/or poor control of the underlying CRS in causing acute exacerbations. Moreover, we have made the novel finding that acute exacerbations may impart a QOL detriment in CRS that is separate from the general baseline sinonasal symptomatology of CRS. This distinction between symptomatology and disease control is important because the primary goal of CRS treatment is to improve QOL.<sup>1,2</sup> Our findings may have important implications for the treatment of CRS in that obtaining better disease control (ie, reducing the frequency of acute exacerbations) may significantly enhance the QOL of patients who suffer from CRS. This may be particularly important for patients who have more severe baseline symptoms in which case reduction in the frequency of acute exacerbations alone may lead to some improvement in QOL.

Our study is the first to describe and characterize the QOL impact of CRS exacerbations, and this has provided new directions for further study, including the efficacy of antibiotics to resolve exacerbations and how oral corticosteroid usage fits into our findings. Future studies are also motivated by the limitations of our study. First, although we have prospectively studied the

association between CRS symptomatology, antibiotic usage, and QOL, we are nonetheless asking patients to retrospectively report their antibiotic usage, which may have introduced recall bias with patients having the severest symptoms being more cognizant of their antibiotic usage. Although asking patients to recall medication usage is common practice for such studies<sup>34</sup> and is also used clinically to make treatment decisions, future studies will ideally track antibiotic usage prospectively. In addition, we did not screen every study participant for immunodeficiency nor did we exclude study participants with immunodeficiency from our study. In our cohort there was one participant found to have a mild IgA and IgG subclass deficiency. We have no *a priori* reason to believe that the negative impact of this individual's CRS exacerbations on QOL is any different than that of study participants without immunodeficiency. However, future studies to further characterize our findings may benefit by stratifying patients with CRS by the presence of immunodeficiency. Moreover, although we may reasonably infer through the correlation of self-reported sinusitis-related antibiotic utilization and sinus infections that antibiotic prescriptions were for acute exacerbations of CRS, the exact indication for each antibiotic course nonetheless could not be definitively established. Although it may be difficult to objectively define criteria for acute exacerbations of CRS, future work will seek to more objectively define that state of patients' CRS at the time of antibiotic prescriptions to definitively understand the physiologic correlate of antibiotic usage that mediates the association between SNOT-22 and general health-related QOL.

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