# Validity of systemic antibiotics and systemic corticosteroid usage for chronic rhinosinusitis as metrics of disease burden*

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## Abstract

**Background**: The frequencies of systemic antibiotics and oral corticosteroids taken for chronic rhinosinusitis (CRS) indicate poor CRS disease control. We sought to determine the validity and responsiveness of these metrics as reflections of CRS disease burden.

**Methodology**: One hundred and eighty-seven patients undergoing medical management for CRS were recruited. Participants were assessed at two time points: enrollment and a follow-up appointment three to nine months later. At each time point, CRS-related antibiotic and oral corticosteroid usage in the previous three months was measured, while general and disease-specific quality of life (QOL) was measured using the visual analog scale of the 5-dimension EuroQol questionnaire (EQ-5D VAS) and the 22-item Sinonasal Outcome Test (SNOT-22), respectively.

**Results**: The frequency of CRS-related antibiotics and oral corticosteroids use was cross-sectionally correlated with EQ-5D VAS and SNOT-22 at the corresponding time points. For participants reporting usage of these medications at enrollment, there was a decrease of 1 course per 3 months for both CRS-related antibiotics and oral corticosteroids. Change in CRS-related antibiotics from enrollment to follow-up was correlated with change in both EQ-5D and SNOT-22 over the same timeframe. The change in CRS-related oral corticosteroids was correlated with change in both EQ-5D VAS and SNOT-22). These correlations were stronger in the subset of patients who had a change in these metrics over the study period.

**Conclusions**: The frequencies of CRS-related antibiotic use and oral corticosteroid use are valid and responsive measures of CRS disease burden.

**Key words**: chronic rhinosinusitis (CRS), antibiotics usage, corticosteroid usage, validation, responsiveness

## Introduction

Chronic rhinosinusitis (CRS) is a common inflammatory disease of the paranasal sinuses[1] that may arise and persist due to heterogeneous etiologies [2-6]. CRS is a significant burden on society, leading to billions of dollars in healthcare costs every year as well as a significant quality of life (QOL) detriment for afflicted patients [7-9]. CRS decreases QOL through various disease manifestations including chronic symptomatology [10,11], acute exacerbations of CRS (AECRS) [12], and exacerbations of comorbid pulmonary disease [11,13,14].

Managing the manifestations of CRS to within acceptable limits is the ideal goal of treatment, whether medical or surgical. The degree to which CRS manifestations are within acceptable limits is referred to as disease control. Criteria for CRS disease control were first proposed by the 2012 European Position Paper on Rhinosinusitis and Polyps (EPOS), which recommended assessment of CRS disease elements such as symptom burden, endoscopic burden of disease as well as the use of systemic antibiotics and

systemic corticosteroids [15]. Subsequent studies have highlighted the potential significance of each of these elements of CRS disease control [16-18]. The chronic symptomatology of CRS (and its burden on patients) as well as nasal endoscopic burden of CRS have been well characterized [11,19-21]. In contrast, systematic antibiotic and systematic corticosteroids usage for CRS as metrics of disease burden are not as well characterized.

The EPOS 2012 criteria describe CRS-related systemic antibiotic usage and systemic corticosteroid usage in the prior 3 months as elements of CRS disease control. Moreover, patient-reported usage of systemic antibiotics and corticosteroids for CRS have been previously described as outcome measures in various studies [22-25]. However, the frequency of patient-reported systemic antibiotic or corticosteroid usage has not been fully validated as both valid and responsive measures of CRS disease burden. Given that patient-reported use of CRS-related antibiotics and systemic corticosteroids are increasingly being used in research as outcomes measures of interest after interventions for CRS and also used as an indicator of overall CRS disease control, it is important to establish whether they serve as representative metrics of the CRS disease burden. In this study, we sought to independently show that general and disease-specific QOL measures are reflected by and responsive to patient-reported CRS-related oral antibiotic and oral corticosteroid usage over the preceding three months.

## Materials and methods

### Study participants

This study was approved by the Massachusetts Eye and Ear Infirmary Human Studies Committee. We prospectively recruited adult patients of age 18 years or older meeting the American Academy of Otolaryngology - Head and Neck Surgery clinical consensus guideline-established criteria for CRS [26]. All study participants provided informed consent for inclusion. Exclusion criteria included comorbid diagnoses of vasculitis, cystic fibrosis, sarcoidosis, immunodeficiency, as well endoscopic sinus surgery within the prior six months.

### Study design and data collection

This was a prospective study of 187 CRS patients undergoing medical management of CRS. All participants were enrolled upon initial presentation to our clinic for CRS. Over the study period, all participants were uniformly treated with intranasal saline irrigations and intranasal corticosteroids, with oral antibiotics or oral corticosteroids given on a patient-by-patient basis, consistent with recommended guidelines for these medications [27]. Data was collected at two time points: at enrollment and at follow-up 3 to 9 months later. Any participant who was a current or former tobacco smoker was considered a smoker for this study [28,29]. At each time point, all participants completed the 22-item Sinonasal Outcome Test (SNOT-22) as a measure of CRS-

specific QOL [30] and the EuroQoL 5-dimensional (EQ-5D VAS) questionnaire from which the visual analog scale (EQ-5D VAS) was used as a measure of general health-related QOL. At each time point, participants were asked to report the number of CRS-related antibiotics and oral corticosteroids they had used in the past 3 months [29,31]. The indications (e.g. AECRS or poor disease control) for CRS-related antibiotics and oral corticosteroids were not recorded. For the purpose of establishing test-retest reliability, a separate set of 15 participants were recruited with follow-up 1 to 3 weeks after the enrollment.

### Statistical analysis

All analyses were performed with the statistical software package R (www.r-project.org). Standard descriptive statistics were performed. All correlations, for example between CRS-related systemic medication usage and measures of QOL, were performed using Spearman correlation. Validation of CRS-related oral antibiotics and oral corticosteroids usage over the previous 3 months was performed by establishing validity, test-retest reliability and responsiveness. Validity was established by showing cross-sectional correlation with SNOT-22 and EQ-5D. Test-retest reliability was assessed by checking for correlation in CRS-related use of oral antibiotics and oral corticosteroids as reported by a set of 15 patients with 1 to 3 weeks between enrollment and follow-up. Responsiveness to medication use was determined by assessing the correlation between change in patient-reported CRS-related oral antibiotics and oral corticosteroids usage and change in SNOT-22 score or change in EQ-5D VAS over the timeframe from enrollment to follow-up.

## Results

### Patient characteristics

A total of 202 participants were included. Of these participants 187 were medically treated for CRS and followed for 3 to 9 months (mean follow-up time 142 days, standard deviation: 49 days). Clinical and demographic characteristics of these participants are summarized in Table 1. At enrollment, 34.2% of participants reported at least one CRS-related oral antibiotics course in the prior 3 months and 23.0% of participants reported at least one CRS-related oral corticosteroids course in the prior 3 months. At follow-up, 20.3% of participants reported least one CRS-related oral antibiotics course and 14.4% of participants reported at least one CRS-related oral corticosteroids course in the prior 3 months.

### Validity of CRS-related oral antibiotic and corticosteroid usage over the prior 3 months

In order to demonstrate validity, we compared patient-reported CRS-related antibiotics and corticosteroids usage at enrollment to SNOT-22 score and EQ-5D VAS (Figure 1). CRS-related antibiotics usage was correlated with SNOT-22 score ($\rho=0.26$, $p<0.001$)

Table 1. Patient characteristics.

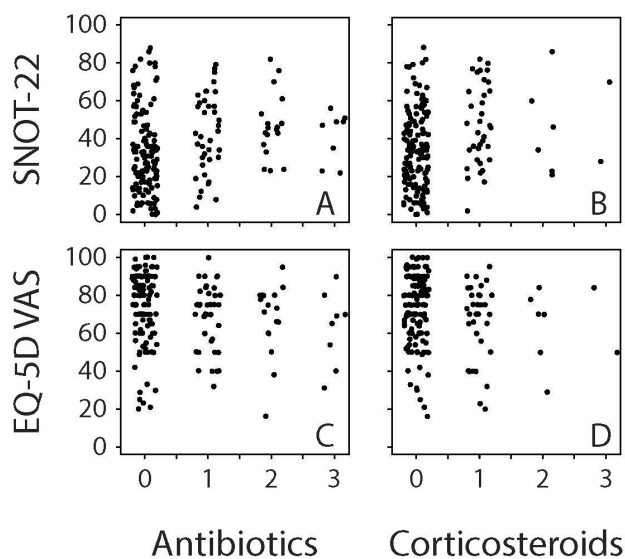| | Study participants (N=187) |
|---|---|
| **Demographics** | |
| Age, mean in years, (SD) | 50.9 (16.6) |
| Gender<br>    Male<br>    Female | <br>49.7%<br>50.3% |
| Smoking | 37.4% |
| **Comorbidities** | |
| Aeroallergen hypersensitivity | 48.7% |
| Asthma | 32.1% |
| Aspirin sensitivity | 4.3% |
| **CRS characteristics at enrollment** | |
| Nasal polyps | 45.5% |
| Previous sinus surgery | 35.8% |
| Intranasal saline use | 24.1% |
| Intranasal corticosteroid use | 43.9% |
| **Patient-reported outcome measures at enrollment** | |
| SNOT-22 score, mean (SD) | 36.9 (21.1) |
| Number of CRS-related antibiotics taken in last 3 months, mean (SD) | 0.5 (0.8) |
| Number of CRS-related oral corticosteroids taken in last 3 months, mean (SD) | 0.3 (0.6) |
| | |
| SNOT-22 score, mean (SD) | 27.3 (18.3) |
| Number of CRS-related antibiotics taken in last 3 months, mean (SD) | 0.3 (0.5) |
| Number of CRS-related oral corticosteroids taken in last 3 months, mean (SD) | 0.2 (0.5) |

SD: Standard deviation



Figure 1. Scatterplots of SNOT-22 score vs. A) reported CRS-related oral antibiotics courses in the prior 3 months and B) reported CRS-related oral corticosteroids courses in the prior 3 months. Scatterplots of EQ-5D vs. C) reported CRS-related oral antibiotics courses in the prior 3 months and D) reported CRS-related corticosteroids courses in the prior 3 months.

and EQ-5D VAS ($\rho$=-0.23, p=0.002). Similarly, at enrollment CRS-related corticosteroids usage was correlated with SNOT-22 score ($\rho$=0.24, p=0.001) and EQ-5D VAS ($\rho$=-0.20, p=0.008).

**Test-retest reliability of CRS-related antibiotic and corticosteroid usage over the prior 3 months**

A set of 15 participants reported their CRS-related antibiotics and oral corticosteroids usage over the prior 3 months at time points 1 to 3 weeks apart. Test-retest reliability was assessed by checking for correlation between participants' responses between the two times points. For this set of 15 participants, the reported CRS-related antibiotics usage over the prior 3 months was significantly correlated ($\rho$=0.85, p<0.001) over the two time points. Also, the reported CRS-related oral corticosteroids usage over the prior 3 months was significantly correlated ($\rho$=0.87, p<0.001).

**Responsiveness of CRS-related antibiotic and corticosteroid usage over the prior 3 months**

Responsiveness was established by assessing the change in reported CRS-related antibiotics and oral corticosteroids usage over the prior 3 months from enrollment to the follow-up time point after the participants had been medically managed for CRS. Over the follow-up period, there was a mean decrease in CRS-related antibiotics usage by 0.3 courses per 3 months and a mean decrease in CRS-related oral corticosteroids usage by 0.1 courses per 3 months. Examining the subset of participants who reported at least 1 course of CRS-related antibiotics in the 3 months prior to enrollment, the mean decrease in CRS-related oral antibiotics usage was 1.2 courses per 3 months over the study period. Likewise focusing on the subset of participants who reported at least 1 course of CRS-related oral corticosteroids in the 3 months prior to enrollment, the mean decrease in CRS-related oral corticosteroids usage was 0.9 courses per 3 months over the study period. Thus with appropriate medical management, the usage of these systemic medications for CRS significantly decreased.

Responsiveness was also established by assessing the correlation between changes in patient-reported CRS-related antibiotics and oral corticosteroids usage over the prior 3 months, and changes in SNOT-22 and in EQ-5D VAS over the 3 to 9 month follow-up period (Figure 2). Over the follow-up period, the change in CRS-related antibiotics usage was correlated with change in SNOT-22 score ($\rho$=0.17, p=0.020) and change in EQ-
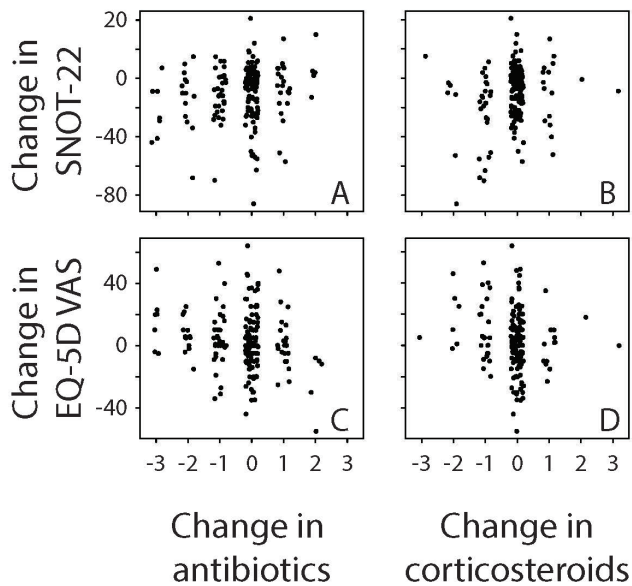
Figure 2. Scatterplots of change in SNOT-22 score vs. A) change in reported CRS-related oral antibiotics courses in the prior 3 months and B) change in reported CRS-related corticosteroids courses in the prior 3 months. Scatterplots of change in EQ-5D VAS vs. C) change in reported CRS-related antibiotics courses in the prior 3 months and D) change in reported CRS-related oral corticosteroids courses in the prior 3 months.

5D VAS (ρ=-0.20, p=0.006). The change in reported CRS-related oral corticosteroids usage was also correlated with change in SNOT-22 score (ρ=0.19, p=0.008) and change in EQ-5D VAS (ρ=-0.16, p=0.030).

## Discussion

Like the treatment of asthma, an inflammatory disorder of the airway which has multiple disease manifestations, the ideal goal of treatment for CRS is to maintain disease manifestations within acceptable limits—to achieve disease control. Although consensus guidelines have been developed for the elements of asthma control and how to distinguish well-controlled asthma from poorly-controlled asthma [32,33], there is yet no such uniformly accepted guidelines for CRS disease control. The 2012 EPOS guidelines provided a major step forward in progress to establish CRS disease control parameters by recommending that a combination of symptom burden, nasal endoscopy and the need for systemic medication (antibiotics and corticosteroids) be considered in the determining how controlled is a patient's CRS and a rubric with which to use these elements to determine a level of CRS disease control [15]. The need for systemic medications indicates poor disease control both because of what it may reflect (greater disease severity or AECRS) but also a direct risk of harm to the patient through the impact of side effects and adverse events. Previous study of systemic medication use for CRS has revealed novel insights into the clinical course of

CRS and also revealed the use of antibiotics and oral corticosteroids for CRS is a distinct aspect of the CRS disease course [12,34-36]. However, patient-reported, CRS-related antibiotics and oral corticosteroids usage has not been validated as a metric for CRS disease burden. In this study, we seek to validate patient-reported, CRS-related antibiotics and oral corticosteroids usage as valid, reliable and responsive measures of disease burden. Previous work has shown that use of antibiotics and oral corticosteroids for CRS is directly associated with reduced QOL as well as productivity [11,12]. The association between the use of these systemic medications and downstream consequences (QOL and productivity) of CRS are independent of other disease aspects, such as symptom burden. For example, the use of CRS-related antibiotics and oral corticosteroids are independently associated with pulmonary exacerbations in asthmatic CRS patients [37] and CRS-related productivity in asthmatic CRS patients [11]. As important elements of the CRS disease course and CRS disease control, validation of CRS-related usage of antibiotics and oral corticosteroids as outcome measured is needed.

In this study, we show that patient-reported, CRS-related antibiotics and oral corticosteroids usages in the prior 3 months are valid, reliable and responsive measures of CRS disease burden. We showed criterion validity by showing that the use of these systemic medications was correlated with general health-related and disease-specific QOL. We showed responsiveness in two ways. First, we show that after the participants used appropriate medical management for their CRS, there was a mean decrease in the usage of CRS-related antibiotics and oral corticosteroids. Of note, when we focused on the subset of participants who had reported at least some usage of these systemic medications at enrollment, appropriate medical management of CRS was associated with a mean decrease of approximately 1 course of each medication per 3 month period. We also showed responsiveness of patient-reported CRS-related antibiotics and CRS-related oral corticosteroids usage in the prior 3 months by showing that the changes in these quantities correlated with changes in general health-related and disease-specific QOL over the study period. Moreover, we find the test-retest reliability of these metrics are quite high. We feel that these results provide credence for the use of these metrics to study and research CRS clinical outcomes. Moreover, the concept of CRS disease control is increasingly being proposed as a unifying measure that synthesizes multiple CRS disease manifestations upon which to base CRS treatment decisions. CRS-related systemic antibiotic and corticosteroid usage in the prior 3 months has been previously recommended as a key component of CRS disease control [15]. Subsequent work has shown that the use of these medications is consistently considered by physicians as a reflection of poor CRS control [18,40]. Our results here also provide support for the use of patient-reported, CRS-related oral antibiotics and oral corticosteroids usages as valid and reliable metrics that can be

used in the clinical setting.

Our results open the door for future study of these metrics to understand the indications for which CRS-related antibiotics and oral corticosteroids are taken. It is very possible that the use of these medications for the resolution of discrete AECRS may be reflective of a different level of disease burden than in the patient whose disease is so severe that these medications are required for suppression of baseline symptomatology, although in both cases patients may be exposed to similar levels of medication-related side effects. This is an exciting area of investigation that will require not only systematic investigation of patient outcomes in each scenario but also consensus building around value judgements related to systemic medication usage as a reflection of poor control due to the underlying indication or the risk of harm (i.e., side effects) to the patient.

Our study should be interpreted in the context of its limitations. Although we show that patient-reported CRS-related usage of oral antibiotics and oral corticosteroids in the past 3 months is reliable, this nevertheless requires patients to recall their usage of these medications which may be influenced by recall bias. The recall period of the SNOT-22 (2 weeks), the EQ-5D VAS (1 day) and CRS-related antibiotics and oral corticosteroids in the past 3 months are all different. However, that we nevertheless find significant correlations speaks to the strength of the relationships between these CRS outcomes. Additionally, the antibiotics and corticosteroids were prescribed by multiple providers, which is a pragmatic aspect of our study design since CRS patients may seek care from any number of physicians. Furthermore, even though general guidelines exist for the use

of these medications the prescription of oral antibiotics and oral corticosteroids for CRS is physician-dependent to some extent. Moreover, the negative impact of oral antibiotics and corticosteroids usage goes beyond poor CRS control but is also reflective of side effects and adverse events that patients may experience from these medications [41,42].

## Conclusion

Patient-reported CRS-related antibiotics and corticosteroids usage are valid and responsive measures of disease burden. CRS disease burden that is reflected by CRS-related antibiotics and oral corticosteroids usage may not only be indicative of poor CRS disease control (e.g. recurrent AECRS or high disease severity) but may also reflect side effects of these systemic medications.

## Acknowledgements

## Authorship contribution

KMP designed and performed the study, and wrote/revised the manuscript; MMS, ETS, RT, DSC, STG performed the study and wrote/revised the manuscript; ARS conceived, designed, and performed the study and wrote/revised the manuscript.

## Conflict of interest

The authors declare no conflicts of interest.

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