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Appropriate Medical Management of Chronic Rhinosinusitis Reduces Use of Antibiotics and Oral Corticosteroids

Marlene M. Speth, MD, MA; Katie M. Phillips, MD; Lloyd P. Hoehle, BS, BA; David S. Caradonna, MD, DMD; Stacey T. Gray, MD; Ahmad R. Sedaghat, MD, PhD

Objectives/Hypothesis: Antibiotics and oral corticosteroids are used in the treatment of acute exacerbations of chronic rhinosinusitis (AECRS) and reflect poor disease control. We sought to characterize utilization of these systemic medications after appropriate medical management of chronic rhinosinusitis (CRS).

Study Design: Prospective observational study.

Methods: One hundred fifty patients undergoing medical management for CRS were studied. Data were collected at enrollment and follow-up 3 to 12 months later. All patients were asked to report the number of CRS-related antibiotics and oral corticosteroids used in the last three months. CRS symptom burden was measured using the 22-item Sino-Nasal Outcome Test (SNOT-22). Associations were sought between CRS-related antibiotics and oral corticosteroids use at follow-up compared to enrollment.

Results: From enrollment to follow-up, the mean number of CRS-related antibiotics courses used decreased by 0.2 courses (95% confidence interval [CI]: 0.1–0.4, P = .012), and the mean number of CRS-related oral corticosteroid courses used also decreased by 0.2 courses (95% CI: 0.1–0.3, P = .029). The number of CRS-related antibiotics used at follow-up was associated with CRS-related antibiotic use at enrollment (adjusted rate ratio [RR] = 1.58, 95% CI: 1.17–2.13, P = .003). The number of CRS-related oral corticosteroids used at follow-up was associated with reported CRS-related oral corticosteroid use at enrollment (adjusted RR = 3.20, 95% CI: 1.69–6.07, P < .001). SNOT-22 results at enrollment were also not predictive of future systemic medication use.

Conclusions: Appropriate medical management of CRS is associated with decreased use of oral antibiotics and corticosteroids. Previous utilization of antibiotics and oral corticosteroids for CRS is associated with future use of these medications.

Key Words: Chronic rhinosinusitis, antibiotics, corticosteroids, acute exacerbations, disease control.

Level of Evidence: 2c

Laryngoscope, 130:E709–E714, 2020

INTRODUCTION

Chronic rhinosinusitis (CRS) is a common inflammatory disease of the paranasal sinuses that affects up to 10% of the population.1–3 The exact mechanisms for and diverse factors influencing development and persistence of the disease may include allergy, poor mucociliary clearance, and immunological dysfunction.4–6 The disease leads not only to a significant health care burden, costing society billions of dollars in direct and indirect costs every year, but also causes a significant quality-of-life (QOL) detriment for affected patients.10–14 Although sinonasal symptomatology associated with CRS is classically considered to be the primary driver of decreased QOL,15,16 prior work has shown that the ability of CRS to exacerbate other comorbid diseases as well as the frequency of acute exacerbations of CRS (AECRS) are also important drivers of decreased QOL.11,17,18 AECRS in particular appear to be distinct clinical manifestations of CRS that negatively affect patients, independent of CRS symptomatology.19,20

One of the major consequences of AECRS is the provision of systemic medications including oral antibiotics and oral corticosteroids, which have consequently been proposed as surrogate measures of AECRS because no formal definition of AECRS has been developed.1,21,22 The use of CRS-related antibiotics and oral corticosteroid use is also included as criteria for CRS disease control in the 2012 European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS2012).1 Previous studies have shown that an increasing frequency of CRS-related antibiotics and oral corticosteroids use, likely as a reflection of AECRS frequency, is independently associated with decreased QOL and poor asthma control.13,15 It is therefore important to understand how the use of these medications may be reduced. It is also important to be able to identify CRS patients who may be most likely to take CRS-related antibiotics and oral corticosteroids in the future. In this study, we studied CRS-related antibiotics and oral corticosteroids use in patients who were started on appropriate medical management, including intranasal saline irrigations.
and intranasal corticosteroids, for CRS. In addition to studying how use of these systemic medications changed with appropriate medical management of CRS, we also sought to determine CRS characteristics that would be associated with future CRS-related antibiotics and oral corticosteroids use. Specifically, we hypothesized that appropriate medical management of CRS would reduce the use of these medications, but that past CRS-related antibiotics, CRS-related oral corticosteroid use, and/or CRS symptom burden may be associated with future use of these systemic medications.

MATERIALS AND METHODS

Study Participants

This study was approved by the Massachusetts Eye and Ear Human Studies Committee. All study participants provided informed consent for inclusion in this study.

Eligibility Criteria

We prospectively recruited adult patients aged 18 years or older meeting the American Academy of Otolaryngology–Head and Neck Surgery clinical consensus guideline-established criteria for CRS who were being treated medically for CRS. To have a homogeneous CRS cohort, our exclusion criteria consisted of comorbid diagnoses of vasculitis, cystic fibrosis, sarcoidosis, immunodeficiency. We also excluded patients taking long-term macrolides given for anti-inflammatory activity to prevent confounding with short-course antibiotics given for antibacterial activity. Endoscopic sinus surgery during the study period was also an exclusion criterion.

Study Design and Data Collection

This is a prospective observational study. Patients undergoing medical management for their CRS were recruited and enrolled upon initial presentation to our clinic for CRS. During the study period, patients were treated medically for CRS using intranasal saline irrigations and intranasal corticosteroids. The frequency, dosing, and distinction between corticosteroid spray versus irrigation was determined on a patient-by-patient basis. Systemic adjunctive medications, such as oral antibiotics or oral corticosteroids, were used on a patient-by-patient basis. All data were collected at two time points: at enrollment and at follow-up 3 to 12 months later. Any participant who was a current or former tobacco smoker was considered a smoker for this study. At enrollment, the presence of comorbid asthma was determined based on guideline criteria, and aerallergen hypersensitivity was determined based on skin or serological testing. The presence of polyps was determined based on nasal endoscopy by the treating rhinologist. All participants completed the 22-item Sino-Nasal Outcome Test (SNOT-22) to measure CRS symptom burden. We used a pragmatic design with respect to assessing CRS-related antibiotics and oral corticosteroids. Our pragmatic study design reflects the real-world assessment of the use of these medications and the reality that patients obtain care for their CRS from multiple providers and at different healthcare systems. Specifically, we asked patients to report the number of CRS-related antibiotics and oral corticosteroids they had used in the past 3 months. Assessing CRS-related antibiotics and oral corticosteroids use over the past 3 months is also consistent with EPOS2012 recommendations for assessing control.

Sample Size Calculation

A sample size calculation was made based on identifying association between independent variables and future CRS-related systemic medication. Multivariable regression models used in this study to detect these associations—and for which this study was powered—included 11 variables. Therefore, a total of 150 participants were recruited to have 90% power at a significance level of .05 to detect an association of medium effect size (Cohen $\delta^2 = 0.15$) between independent variables and future CRS-related systemic medication use using our multivariable models.

Statistical Analysis

All analyses were performed with the statistical software package R (www.r-project.org; The R Foundation for Statistical Computing, Vienna, Austria). Standard descriptive statistics were performed. Negative binomial regression was performed to determine whether CRS-related antibiotics use, CRS-related oral corticosteroids use, and SNOT-22 score at enrollment (as independent variables) would be associated with the use of CRS-related antibiotics and oral corticosteroids at follow-up (as dependent variables). Multivariable models used to study these associations controlled for participant age, gender, polyps, asthma, history of smoking, history of allergic rhinitis, intranasal corticosteroid use, and history of previous endoscopic sinus surgery.

RESULTS

Patient Characteristics

In total, 150 patients participated in the study; their clinical and demographic characteristics are described in Table I. At enrollment, the mean SNOT-22 score was 33.5 (standard deviation [SD] = 22.9), the number of CRS-related antibiotics courses used during the last 3 months was 0.5 (SD = 0.9), and the number of CRS-related oral corticosteroid courses used during the last 3 months was 0.3 (SD = 0.7). At enrollment, 33.3% of participants were using intranasal saline irrigations, and 52.7% of participants were using at least some form of intranasal corticosteroid. The mean length of time between enrollment and the next follow-up visit was 184 days (SD = 85 days). At the follow-up visit, the mean SNOT-22 score was 23.9 (SD = 19.6), the number of CRS-related antibiotics courses reported to have been used during the preceding 3 months was 0.3 (SD = 0.6), and the number of CRS-related oral corticosteroid courses reported to have been used during the last 3 months was 0.1 (SD = 0.5).

CRS-Related Systemic Medication Use Decreases With Appropriate Medical Management of CRS

The mean number of CRS-related antibiotics courses used decreased by 0.2 courses (95% confidence interval [CI]: 0.1–0.4) over the study period, when the study participants were medically managed for their CRS. This represented a statistically significant decrease ($P = .012$). The mean number of CRS-related oral corticosteroid courses used also decreased by 0.2 courses (95% CI: 0.1–0.3) over the study period, which also represented a statistically significant decrease ($P = .029$).

Past CRS-Related Antibiotics Use Predicts Future CRS-Related Antibiotics Use

We first checked to see if CRS-related antibiotics use, CRS-related oral corticosteroids use, and/or SNOT-22
score at enrollment would be associated with CRS-related antibiotics use reported at the follow-up time point (Table II). On univariate analysis, only frequency of CRS-related antibiotics use reported at enrollment (RR = 1.46, 95% CI: 1.09–1.94,  \( P = .010 \)) was associated with CRS-related antibiotics use at follow-up. By contrast, the frequency of CRS-related antibiotics use at follow-up was not associated with SNOT-22 score at enrollment (RR = 1.01, 95% CI: 0.99–1.02, \( P = .364 \)) or the frequency of CRS-related oral corticosteroids use at enrollment (RR = 1.26, 95% CI: 0.81–1.94, \( P = .301 \)). These associations were confirmed using our multivariable model, which found that a greater frequency of CRS-related antibiotics at follow-up was only associated with the frequency of CRS-related antibiotics use reported at enrollment (RR = 1.61, 95% CI: 1.16–2.24, \( P = .004 \)) but not SNOT-22 score at enrollment (RR = 1.00, 95% CI: 0.98–1.02, \( P = .914 \)) or the frequency of CRS-related oral corticosteroids use at enrollment (RR = 0.93, 95% CI: 0.57–1.51, \( P = .782 \)).

### TABLE I.
Clinical and Demographic Characteristics of Study Participants.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>All Study Participants, ( N = 150 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, mean (SD)</td>
<td>51.9 (14.8)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>54.7%</td>
</tr>
<tr>
<td>Female</td>
<td>45.3%</td>
</tr>
<tr>
<td>Smoking</td>
<td>28.7%</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>Aeroallergen hypersensitivity</td>
<td>45.3%</td>
</tr>
<tr>
<td>Aspirin sensitivity</td>
<td>4.0%</td>
</tr>
<tr>
<td>Asthma</td>
<td>36.0%</td>
</tr>
<tr>
<td>CRS characteristics</td>
<td></td>
</tr>
<tr>
<td>Nasal polyps</td>
<td>51.3%</td>
</tr>
<tr>
<td>Previous sinus surgery</td>
<td>41.3%</td>
</tr>
<tr>
<td>Patient-reported outcome measures at enrollment</td>
<td></td>
</tr>
<tr>
<td>SNOT-22 score, mean (SD)</td>
<td>33.5 (22.9)</td>
</tr>
<tr>
<td>No. of CRS-related antibiotics taken in last 3 months, mean (SD)</td>
<td>0.5 (0.9)</td>
</tr>
<tr>
<td>No. of CRS-related oral corticosteroids taken in last 3 months, mean (SD)</td>
<td>0.3 (0.7)</td>
</tr>
<tr>
<td>Patient-reported outcome measures at follow up</td>
<td></td>
</tr>
<tr>
<td>SNOT-22 score, mean (SD)</td>
<td>23.9 (19.6)</td>
</tr>
<tr>
<td>No. of CRS-related antibiotics taken in last 3 months, mean (SD)</td>
<td>0.3 (0.6)</td>
</tr>
<tr>
<td>No. of CRS-related oral corticosteroids taken in last 3 months, mean (SD)</td>
<td>0.1 (0.5)</td>
</tr>
</tbody>
</table>

Mean follow-up time = 184 days (SD = 85 days).
CRS = chronic rhinosinusitis; SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test.

### TABLE II.
Association With Courses of CRS-Related Systemic Medications Reported at Follow-up.

<table>
<thead>
<tr>
<th>CRS-related antibiotics at follow-up</th>
<th>Univariate</th>
<th>Multivariable*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>( P ) Value</td>
</tr>
<tr>
<td>Courses of CRS-related antibiotics use at enrollment</td>
<td>1.46 (1.09-1.94)</td>
<td>.010</td>
</tr>
<tr>
<td>Courses of CRS-related oral corticosteroids use at enrollment</td>
<td>1.26 (0.81-1.94)</td>
<td>.301</td>
</tr>
<tr>
<td>SNOT-22 at enrollment</td>
<td>1.01 (0.99-1.02)</td>
<td>.364</td>
</tr>
<tr>
<td>CRS-related corticosteroids at follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Courses of CRS-related antibiotics use at enrollment</td>
<td>1.51 (0.89-2.57)</td>
<td>.124</td>
</tr>
<tr>
<td>Courses of CRS-related oral corticosteroids use at enrollment</td>
<td>2.79 (1.48-5.28)</td>
<td>.002</td>
</tr>
<tr>
<td>SNOT-22 at enrollment</td>
<td>1.02 (0.99-1.04)</td>
<td>.261</td>
</tr>
</tbody>
</table>

*Multivariable model includes the following variables recorded at enrollment: age, gender, history of smoking, aeroallergen hypersensitivity, asthma, nasal polyps, prior endoscopic sinus surgery, intranasal corticosteroid use, courses of CRS-related antibiotics within the previous 3 months, courses of CRS-related oral corticosteroids within the previous 3 months, SNOT-22 score. 
CI = confidence interval; CRS = chronic rhinosinusitis; RR = rate ratio; SNOT-22 = 22-item Sino-Nasal Outcome Test.
DISCUSSION

CRS-related antibiotics and oral corticosteroids use is a reflection of AECRS frequency as well as CRS disease control, as recommended by EPOS2012.\textsuperscript{1,28} AECRS are important inasmuch as they can have a significant detrimental impact on patients with CRS, ranging from diminishing QOL to reducing productivity.\textsuperscript{11,19,29} CRS disease control is a global metric of CRS that may be used for clinical decision making regarding maintenance and escalation or de-escalation of treatment.\textsuperscript{1,28,29} For these reasons, it would be of great utility to understand how CRS-related antibiotics and oral corticosteroids use may be curbed with appropriate medical management but also to predict future use by understanding factors associated with them. The ability to identify patients at the highest risk for future AECRS and poor disease control would allow more personalized management through counseling patients about their expected CRS disease course or identification and avoidance of possible triggers (e.g., aeroallergens for the hypersensitive patient), closer monitoring of patients, or even consideration for more aggressive upfront treatment.\textsuperscript{1,31} In this study, our goal was to study how appropriate medical management of CRS would impact CRS-related antibiotics use and CRS-related oral corticosteroids use as well as to identify factors that would be predictive of their future use. We found that appropriate medical management of CRS, consisting of intranasal saline and intranasal corticosteroids, was significantly associated with decreased CRS-related antibiotics use and CRS-related oral corticosteroids use. We also found that past CRS-related antibiotics use was associated with future CRS-related antibiotics use, whereas past CRS-related oral corticosteroid use was associated with future CRS-related oral corticosteroid use. Moreover, SNOT-22 score was not associated with future use of either CRS-related antibiotics or oral corticosteroids.

Previous studies have demonstrated that AECRS are distinct clinical manifestations of CRS, impacting QOL and asthma control, independent of chronic symptom burden.\textsuperscript{11,19} The independent impact of AECRS also suggests the possibility of independent mechanisms for AECRS. In this study, we investigated CRS-related antibiotics and systemic corticosteroids use, which may serve as an indirect measure of AECRS, in a cohort of medically managed CRS patients. We found that appropriate medical management of these CRS patients led not only to a decrease in symptoms (i.e., SNOT-22 score) but also a decrease in the use of CRS-related antibiotics and systemic corticosteroids. We also found that past CRS-related antibiotics use is associated with future CRS-related antibiotics use, whereas past CRS-related oral corticosteroid use is associated with future CRS-related oral corticosteroid use, independent of CRS symptom burden (i.e., SNOT-22 score), which was not at all associated with future CRS-related systemic medication use. Interestingly, past use of neither medication was associated with future use of the other. The results of our study highlight the importance of appropriate medical management for decreasing CRS-related systemic medication use, provide novel clinical insights for identifying patients most prone to future development of AECRS and poor CRS control, and also provide even more evidence that AECRS are distinct clinical manifestations of CRS.

Our results may also be reflective of recent work demonstrating the challenges of medical treatment of CRS in the primary care setting, where participants in our study were likely getting most of their antibiotics and oral corticosteroids prior to enrollment. With respect to the use of intranasal saline or intranasal corticosteroids, patients report challenges with adherence and using these medications on a regular basis.\textsuperscript{32} Moreover, there may be a lack of adherence by general practitioners to guideline-established medical management of CRS, including overprescribing antibiotics for CRS in the primary care setting.\textsuperscript{33,34} It is also possible that our study reflects the positive benefits of CRS management by specialists, from greater explanation of how to use topical medications, which may improve adherence, to greater guideline-directed treatment of CRS, including more conservative use of antibiotics and oral corticosteroids. Our results, which show CRS-related antibiotics and oral corticosteroids use to be elements of the disease process that are independent of chronic symptom burden, support previous studies that have identified putative inflammatory mediators or triggers that may drive the frequency of AECRS as distinct pathologic phenomenon.\textsuperscript{35–37} Although the pathophysiology of AECRS is still poorly understood, previous studies suggest that immunological changes might play a profound role with levels of interleukin (IL)-5, IL-6, IL-33, and eosinophil major basic protein increasing during an AECRS,\textsuperscript{36} especially in patients with nasal polyps.\textsuperscript{35}

The findings of our study have important clinical implications. First of all, our results show that appropriate medical management of CRS may lead to decreased use of antibiotics and oral corticosteroids for CRS. Moreover, as AECRS are increasingly gaining traction as important but understudied aspects of the CRS disease course, and CRS disease control is recognized as an important metric of disease burden, the ability to identify patients with increased predilection for CRS-related antibiotics and oral corticosteroids use may lead to more personalized management. Our results show that poor CRS disease control due to AECRS requiring systemic medication is predictive of poor CRS disease control due to AECRS in the future, potentially reflective of exacerbation-prone CRS patients\textsuperscript{38} which may be accounted for in the decision to maintain or escalate management. There remains, however, a knowledge gap in terms of our understanding of the pathophysiology that may drive AECRS requiring the use of CRS-related antibiotics and oral corticosteroids. Further research is needed to identify biomarkers reflective of AECRS pathophysiology and predictive of the need for CRS-related systemic medication use.

Our study should be interpreted in the context of its limitations. Although CRS-related antibiotics and corticosteroid use represents a surrogate measure for AECRS, these are nevertheless indirect measures, and there are
likely patients suffering from AECRS without any systemic medication use. Therefore, our results do not provide insights for predicting all exacerbation-prone patients. Our study design excluded patients on long-term immunomodulatory macrolides; study of this patient population in the future may provide additional insights not reported here. Moreover, our pragmatic study design and methodology to ask patients about CRS-related antibiotics and oral corticosteroids use in the past 3 months may be subject to recall bias. Additionally, it may be asked whether our findings are simply a reflection (or artifact) of physician practice patterns. One could posit that participants who were more likely to use each type of systemic medication were being treated by physicians who were more likely to prescribe those medications. This is a possibility because we did not mandate that participants receive CRS-related systemic medications only from us between enrollment and follow-up. However, because enrollment took place at the initial presentation to our clinics, participants' reported baseline medication use at enrollment was reflective of medication prescriptions by referring physicians and not our group. By contrast, after enrollment, the majority of CRS-related medication was prescribed by our group and therefore under different practice conditions.

CONCLUSION

Appropriate medical management of CRS is associated with decreased CRS-related use of antibiotics and oral corticosteroids. The use of CRS-related antibiotics and oral corticosteroids is associated with the past use of those medications, respectively. The SNOT-22 score, reflective of chronic sinonasal symptom burden associated with CRS, was not associated with future CRS-related antibiotics or oral corticosteroids use reported by patients. Based on implications for CRS disease control, the prognostic significance of our results may be considered in the determination of CRS treatment plans.

ACKNOWLEDGMENTS

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BIBLIOGRAPHY


