Published in final edited form as:

Int Forum Allergy Rhinol. 2017 April ; 7(4): 343–351. doi:10.1002/alr.21903.

Examination of high-antibiotic users in a multi-institutional cohort of CRS patients

Vijay R. Ramakrishnan, MD¹, Jess C. Mace, MPH, CCRP², Zachary M. Soler, MD, MSc³, and Timothy L. Smith, MD, MPH²

¹Department of Otolaryngology, University of Colorado, Aurora, CO

²Department of Otolaryngology-Head and Neck Surgery, Oregon Health Sciences University, Portland, OR

³Department of Otolaryngology-Head and Neck Surgery, Medical University of South Carolina, Charleston, SC

Abstract

Background—In addition to known concerns regarding antibiotic overuse, recent research indicates that excessive antibiotic use is associated with poorer long-term health. Given that rhinosinusitis is the leading condition accounting for antibiotic prescriptions in the ambulatory setting, we aimed to evaluate characteristics associated with greater antibiotic use in CRS.

Methods—Adult CRS patients enrolled in a prospective, multi-institutional, observational cohort study evaluating treatment outcomes were included in this analysis. Study participants were asked to report the number of days out of the previous 90 days that systemic antibiotics were taken for sinus disease. Patient demographics, disease characteristics, and measures of disease severity were evaluated.

Results—561 patients from 4 institutions were included in the analysis, with mean antibiotic use of 17.4 $\pm$ 22.4 out of the prior 90 days. No differences between antibiotic-use groups were found for objective measures of disease severity (CT, endoscopy, BSIT scores), however, increased patient-reported symptom burden (SNOT-22, RSDI) was associated with more antibiotic use. Patients reporting the most antibiotic use were older ($p=0.004$) but no ethnic or gender differences were seen. Comorbid diagnoses of allergy, asthma, diabetes, depression, or fibromyalgia, were not associated with increased antibiotic use. In accordance with literature recommendations, CRSwNP patients were less likely to have used antibiotics. ESS significantly decreased antibiotic use.

Conclusion—Variability in antibiotic use in CRS appears to be driven by symptom burden, independent of objective measures of disease severity, patient demographics, and presence of comorbid disease. Clear guidelines are essential to define appropriate antibiotic use in CRS.

Corresponding author: Vijay R. Ramakrishnan, MD, Department of Otolaryngology, University of Colorado, 12631 E 17th Ave, B205, Aurora, CO. 80045, **Phone:** 303-724-1965, **Fax:** 303-724-1961, Vijay.Ramakrishnan@ucdenver.edu.

The abstract for this manuscript was accepted for oral/podium presentation to the American Rhinologic Society during the American Academy of Otolaryngology-Head and Neck Surgery annual meeting in San Diego, CA., 16–17th, 2016.

MeSH Key words

sinusitis; anti-bacterial agents; prospective studies; outcome assessment (health care); multicenter study; endoscopy

INTRODUCTION

Chronic rhinosinusitis (CRS) is generally regarded as a medical disease in which management consists of numerous medical therapies prior to consideration for surgery [1], however, there is no consensus for what constitutes appropriate or “maximal” medical therapy. A number of guidelines consider antibiotics as part of maximal medical therapy for CRS [2,3], with most studies of maximal medical therapy in CRS utilizing a three-week antibiotic course, though there is significant variation in duration [4]. Although CRS is now widely understood to be an inflammatory disease, the potential for infectious origin or exacerbation, coupled with historical doctrine, have led to a paradigm where antibiotics are often used in a prolonged or repeated fashion. Guidelines are notably inadequate here, and evidence-based consensus statements [1,5] have left general antibiotic use open as an “option” for therapy. As such, antibiotic use in the medical management of CRS is largely left to the provider’s discretion.

Antibiotics have earned a part in the medical regimen for CRS, and may be a necessary component of therapy in certain patients or at certain times when bacterial overgrowth contributes to disease exacerbation. However, antibiotic use has a number of potential negative effects. Many serious individual and societal concerns exist for antibiotic overuse, including a newly demonstrated long-term health hazard mediated through a hypothesized microbiome disturbance, most readily observed in infants who have yet to establish a stable and resilient gut microbiome [6]. It remains to be seen if these effects occur in adulthood, or perhaps in certain susceptible adults. More well-established antibiotic-associated detrimental effects to the individual exist, including cost to the patient, risk of side effects including *C.difficile* colitis, and potential for development of drug-resistance [7]. Similarly, system-wide costs and development of resistant organisms are major concerns. Drug-resistant organisms are associated with increased risk of hospitalization, need for ICU care, prolonged hospital stay, increased hospital costs, and risk of death [8,9]. The emergence of drug-resistant organisms coupled with major challenges in novel antibiotic development have driven a widespread tightening of indications for, and duration of, antibiotic use [10]. As a highly prevalent condition managed by providers in many different settings, with loose regulation for antibiotic therapy, an understanding of which patients utilize the most antibiotics in CRS would be a useful first step in establishing a paradigm for responsible use of antibiotics in this disease process.

Understanding that there is a variable and ill-defined role for antibiotics in medical therapy for CRS, the objective of this study is to examine patient and disease characteristics associated with increased antibiotic use in CRS.

MATERIALS and METHODS

Study Population and Inclusion Criteria

Adult study patients (≥ 18 years old) were recruited as part of a prospective, multi-center, observational cohort study developed to evaluate treatment outcomes of endoscopic sinus surgery (ESS). All study patients were diagnosed with medically refractory CRS as endorsed by both the American Academy of Otolaryngology-Head and Neck Surgery 2007 guidelines and the European Position Paper on Rhinosinusitis and Nasal Polyps 2012 (EPOS 2012) [5, 11]. The Institutional Review Board (IRB) at each performance site governed all study protocols, informed consent documentation, and data safety monitoring. Performance sites consisted of tertiary care sinus surgery centers located within academic hospital systems in North America including: Oregon Health & Science University (OHSU; Portland, OR; eIRB#7198), Stanford University (Palo Alto, CA; IRB#4947), the Medical University of South Carolina (Charleston, SC; IRB#12409), and the University of Calgary (Calgary, Alberta, Canada; IRB#E-24208), with central study coordination at OHSU.

Study participants voluntarily selected ESS as the subsequent treatment option for mitigation of symptoms related to CRS following previous attempts at medical therapy including, but not limited to, at least one course of either topical corticosteroids (≥ 21-days) or a 5-day course of oral corticosteroid therapy, and at least one course (≥ 14-days) of culture-directed or broad spectrum antibiotic therapy administered at any time in the past for CRS. Study enrollment meetings occurred after study participants elected ESS, during which participants were screened for demographics, social and medical history including factors listed in Table 1. Participants were followed postoperatively through the standard of care for up to 18-months and asked to complete postoperative, study evaluations at regular 6-month intervals, either during physician-directed appointments or follow-up study mailings utilizing the postal service and self-addressed return envelopes. Findings from this cohort study have been previously reported [12–15].

Endoscopic Sinus Surgery

The degree of surgical intervention was determined by the intraoperative discretion of each enrolling physician, reflecting individual patient requisites and disease progression. Study participants were either primary or revision ESS cases. Procedural types included unilateral or bilateral maxillary antrostomy, total or partial ethmoidectomy, sphenoidotomy, or frontal sinusotomy procedures (Draf IIa, IIb, or III), with either adjunctive inferior turbinate reduction or septoplasty as guided by symptoms, anatomy, and disease. Intraoperative image guidance visualization was used selectively according to AAO-HNS indications and surgeon discretion. Postoperative therapeutic regimens were prescribed as needed but, at a minimum, included 240ml of daily low-pressure nasal saline irrigation to promote optimal postoperative healing [16].

Exclusion Criteria

Participants were considered lost to follow-up if no postoperative evaluations were provided within 18 months after the date of ESS. Additionally, subjects with any variant of comorbid

cystic fibrosis or ciliary dyskinesia were excluded from final analysis due to variations in global health and differential treatment considerations surrounding their standard of care.

Objective Measures of Disease Severity

Diagnostic measures of disease severity, collected as part of the standard of care, were used simultaneously for investigational purposes. Sinonasal endoscopy exams were completed with a 0–30° rigid endoscope and staged by each enrolling physician using the Lund-Kennedy endoscopy scoring system [17]. Study participants also provided high-resolution computed tomography (CT) radiographic imaging of the paranasal sinuses. Each enrolling physician reviewed CT images for diagnostic purposes and staged each image using the Lund-Mackay scoring system [18]. Olfactory function and detection was measured during each study evaluation time point using the BSIT (Sensonics Inc., Haddon Heights, NJ.) instrument. Higher BSIT total scores (score range: 0–12) reflect a better sense of smell [19,20].

Patient Reported Outcome Measures

The first patient reported outcome measures (PROMs) used in this investigation was the 22-item SinoNasal Outcome Test (SNOT-22), a validated instrument developed to quantify symptom severity associated with sinonasal conditions (©2006, Washington University, St. Louis, MO) [21,22]. Previous factor analysis of the SNOT-22 items has identified 5 distinct domains including: rhinologic symptoms (score range: 0–30), extra-nasal rhinologic symptoms (score range: 0–15), ear / facial symptoms (score range: 0–25), psychological dysfunction (score range: 0–35), and sleep dysfunction (score range: 0–25) [23].

The second utilized PROM was the Rhinosinusitis Disability Index (RSDI), a 30-item survey instrument developed to quantify symptom severity associated with CRS in a complimentary fashion. The RSDI is comprised of 3 domains that evaluate the impact of CRS on a patient's physical (range: 0–44), functional (range: 0–36), and emotional (range: 0–40) domains [24]. The enrolling physician/surgeon was blinded to survey responses for the entire study duration.

PROM data were collected at the time of study enrollment, and at post-treatment follow-up visits.

Prescribed Systemic Antibiotic Use

Study participants were asked to recall medication use specifically prescribed for treatment of their symptoms related to CRS. As the primary exposure variable of interest to this investigation, study participants reported the number of days out of the previous 90 days that they had taken systemic antibiotics for sinus-related indications. This was assessed at study enrollment prior to ESS, and at final follow-up evaluation (mean 14.9, range 4–29 months).

Data Management and Statistical Analyses

Protected health information was removed and study data was safeguarded using unique study identification number assignment for each participant. Study data was securely transferred to OHSU from each performance site for manual entry into a HIPAA compliant,

relational database (Access, Microsoft Corp, Redmond, WA.). All statistical analyses were completed using commercially available software (SPSS, IBM Corporation, Armonk, NY.). Study data were evaluated descriptively while continuous and ordinal variables were evaluated for assumptions of normality. Reported preoperative antibiotic use days was considered the primary exposure of interest and stratified into approximate quartiles to maximize statistical power and sensitivity between independent groups. Days of postoperative antibiotic use was defined using the last available postoperative evaluation (6 months postoperatively). Covariate and PROM differences between antibiotic use groups were evaluated using analysis of variance (ANOVA), Kruskal-Wallis testing, and Pearson's chi-square (χ^2) omnibus testing with adjustments for multiple comparisons where appropriate. Postoperative within-subject improvement in average antibiotic use days was also evaluated using paired sample t-testing. Further evaluation of PROMs was conducted using simple stepwise linear regression to allow for basic adjustment for significant cofactors across antibiotic use groups. Confounding was defined by alteration in the effect estimate (β) of the antibiotic group variable of at least 10% with covariate model inclusion. Statistical comparisons were reported using a type-I error probability at the 0.050 level of significance.

RESULTS

Final Cohort Characteristics

A total of 561 study participants met all inclusion criteria and were prospectively enrolled between April 2011 and July 2015. Postoperative prescribed antibiotic use data were collected for 427 out of 434 (77%) study participants that completed follow-up at a mean of 14.9 [5.1] months. Study participants with follow-up reported an average of 17.4 [22.4] days of preoperative antibiotic use [median 10.0 days] out of the prior 90 days at enrollment, compared to 19.9 [23.9] days [median 14.0 days] for study participants without follow-up ($p=0.244$). Demographics and comorbid disease characteristics, stratified across preoperative antibiotic use groups, are described in Table 1 for participants with follow-up while the prevalence of ESS interventional procedures are described in Table 2. The overall mean age for the final cohort was 51.0 [15.4] years with a median of 53.0 years. Results from omnibus testing found that study participants who reported 1–14 days of antibiotic use prior to surgery were significantly younger than participants reporting 29+ days of preoperative antibiotic use ($p=0.004$) after adjustment for multiple comparisons. Similarly, participants reporting no preoperative antibiotic use were found to have a significantly higher prevalence of CRSwNP compared to groups reporting 15–28 days of antibiotic use ($p=0.010$) and 29+ days of antibiotic use ($p<0.001$) after adjustment for multiple comparisons. Study participants reporting 1–14 days of antibiotic use were also found to have greater prevalence of CRSwNP compared to 29+ days of preoperative antibiotic use ($p=0.037$). Respiratory comorbidities such as allergies, asthma, and aspirin sensitivity were *not* associated with increased antibiotic use, neither were unrelated comorbid diagnoses of fibromyalgia, depression, or diabetes. Draf III frontal sinusotomy procedures were uncommonly performed, however, patients undergoing this type of frontal surgery were more likely to have had more extensive antibiotic use.

Antibiotics and PROMs

Clinical measures of disease severity and PROM scores, stratified across preoperative antibiotic use groups, are described in Table 3. Antibiotic use was associated with significantly worse overall SNOT-22 scores, however, this finding primarily resulted from the four *non*-rhinologic symptom domains. After adjustment for multiple comparisons, study participants with 1–14 days of preoperative antibiotic use reported significantly worse mean SNOT-22 extra-nasal rhinologic and ear/facial symptom domain scores compared to participants without any preoperative antibiotic use ($p = 0.028$; Table 3). Study participants with the heaviest antibiotic use (29 or more days) also reported significantly worse mean SNOT-22 psychological dysfunction scores compared to participants without preoperative antibiotic use ($p = 0.002$). Similarly, participants reporting 15–28 days and 29 or more days of antibiotic use also reported significantly worse mean sleep dysfunction domain scores of the SNOT-22 compared to without antibiotic use ($p = 0.040$). Significant associations between preoperative PROM scores and antibiotic use groups all still remained after controlling for polyp status with linear regression modeling. No evidence of significant confounding by nasal polyposis of any preoperative PROM score between antibiotic use groups was evident.

Participants in the two highest antibiotic use groups (15–28 days and 29 or more days) also reported significantly worse mean RSDI total scores, as well as worse RSDI physical domain and emotional domain scores, compared to participants without antibiotic use ($p = 0.016$). Participants without preoperative antibiotic use also reported significantly better mean RSDI functional domain scores compared to all other antibiotic use groups ($p = 0.026$) after adjustment for multiple comparisons.

No significant differences between any antibiotic use groups were found for any clinical measure of disease severity.

Institutional Differences of Antibiotic Use

The prevalence of preoperative antibiotic administration was compared across institutions, which consisted of tertiary care specialty Rhinology practices with providers well-trained in current guidelines for antibiotic use. Average antibiotic use days between enrollment sites ranged from 14.5[18.8] to 22.8[24.4] days. After adjustment for multiple comparisons, no significant difference in preoperative antibiotic use days was evident between any two enrollment sites ($p = 0.064$).

Effects of ESS on Antibiotic Use

After endoscopic sinus surgery, average days of reported antibiotic use (out of the previous 90 days) significantly ($p < 0.001$) decreased from 17.4[22.4] to 6.9[16.9] when examining all subjects with follow-up. Significant within-subject decreases in mean antibiotic use days were reported across all preoperative antibiotic use groups other than the zero-use group, presumably to the use of antibiotics in the immediate postoperative setting (Table 4).

DISCUSSION

The heterogeneous nature of CRS, where some cases are suspected by the physician (and sometimes patient) to exhibit a significant infectious bacterial component, is reflected in the noncommittal literature on antibiotic use in CRS [25, 26]. The findings from the current study are consistent with the literature, demonstrating variability likely due to the lack of defined criteria for which CRS patients should receive antibiotics, for how long, and for how many attempts before making the decision to move forward with procedural intervention. It is important to note that antibiotic use was less in the CRS with polyp population, demonstrating an incorporation of recent understanding of CRS pathophysiology and clinical recommendations into direct patient care. In this large cohort, antibiotic use did not correlate with objective measures of disease severity outside of polyp status, and appeared more so to be driven by patient perception of severity. It is possible that antibiotic therapy is more useful in certain CRS phenotypes, such as biofilm-mediated disease, chronic *S.aureus* or *P.aeruginosa*, osteitis, or refractory frontal sinusitis, and future outcomes studies regarding antibiotic use in CRS may need to account for these phenotypic variations. Prior studies examining the benefits of ESS on antibiotic use have demonstrated significant overall benefit, as measured by the Chronic Sinusitis Survey question regarding the number of weeks out of the prior 8 weeks that the patient has used antibiotics [27,28]. Our current data supports this finding, and adds to it by demonstrating a greater benefit for decreased antibiotic use after ESS for patients that are high preoperative utilizers. This information may be of benefit in counseling patients preoperatively, and even in shared clinical decision-making when debating if ESS is worth pursuing.

Our examination of antibiotic use in a large, multi-institutional, cohort of refractory CRS patients sheds some interesting light on the question of which patients utilize the most antibiotics. Older patients were more likely to use antibiotics frequently, perhaps suggesting that these patients are more comfortable with the traditional doctrine of antibiotic therapy for CRS, or that providers are more willing to continue medical therapies rather than proceeding to ESS in the older population. Surprisingly, the presence of comorbidities such as allergy, asthma, depression, fibromyalgia, and diabetes, were not associated with more antibiotic use. This finding seems counterintuitive, but perhaps both patients and providers were willing in these scenarios to move up the algorithm to ESS without continuing or prolonging medical therapies in efforts to gain whatever possible benefit is achievable with ESS, aware of outcomes data demonstrating comparable sinus- and health-related improvement in these patient populations [29–33]. Notably, *objective* measures of disease severity (eg, CT scan, endoscopy findings, and SIT score) were *not* associated with antibiotic use, whereas patient-reported symptoms were most associated with antibiotic use. This might be surprising on first glance, suggesting that medication prescribers may not account for the degree of objective disease burden when making the decision to administer antibiotics. Rather, the finding that antibiotic usage correlated with patient-reported symptom burden is consistent with prior evidence that patient-reported symptom severity is a large driver of therapeutic decision making, particularly in regards to electing to pursue surgical intervention [23, 34]. Even so, when examining subdomains of the SNOT-22 and RSDI, non-rhinologic domains were most associated with antibiotic use. This suggests that patients who are particularly

bothered by symptoms beyond the local sinonasal region may seek more therapeutic medical interventions, and/or that prescribers whose patients complain of bothersome extra-rhinologic symptoms are more willing to offer antibiotic therapy. It is certainly possible that patients who appear to be the most bothered by disease may more often receive antibiotics from their providers as a result of alternate motivations such as perceived patient expectation and satisfaction, or to facilitate a timely and simple conclusion to a lengthy office visit.

In a national database study of ambulatory care antibiotic prescriptions, CRS accounted for 7.1% of all antibiotic prescriptions, more than any other primary diagnosis [35]. Risks for development of drug resistant organisms is of significant concern to the individual in CRS--prior studies have shown drug resistance in greater than 60% of CRS cases, with 19% of *S.aureus* strains exhibiting methicillin resistance [36,37]. This number appears to be even higher in more recent studies, approaching 90% in one report of CRS patient cultures [38]. In fact, the World Health Organization has described the development of drug-resistant organisms as one of the three greatest threats to human health. Of additional interest in CRS, subtherapeutic or repeated antibiotic doses reaching the sinuses may paradoxically increase bacterial pathogenicity and induce drug resistance, mediated by selection of resistant organisms, increased bacterial mutagenesis, induction of virulence genes, and release of pro-inflammatory factors [39–43]. In addition to the well-documented individual and societal concerns for general antibiotic overuse, including cost, side effects, and drug resistance, new data indicates a potential long-term deleterious microbiome effect for frequent antibiotic use, at least in infancy [6]. A diverse and stable microbiome contributes to healthy immune system function, and degradation in the microbiome appears to be a risk factor for allergic and autoimmune diseases, at least in the microbiome establishment of early life [44–47]. This novel concept has been documented in laboratory animals [48,49], and has also been observed in antibiotic-originated microbiome disturbances in human infants where susceptibility to long-term gut microbial disturbances is highest. Although these findings have not been confirmed in studies of adult sinuses, the adult human microbiome has a variable degree of susceptibility to perturbation [50–52], and with the high degree of antibiotic use in this refractory CRS population (average of 17 out of 90 days antibiotic use), some portion of the population may be at risk for long-term detrimental effects from this degree of antibiotic use.

Although there are clear guidelines outlining the use of antibiotic therapy in acute bacterial rhinosinusitis, current AAO-HNS guidelines do not offer any recommendation or discussion for the use of antibiotics in CRS and refer to this as a “*research need*” [16]. The recent International Consensus Statement on Rhinosinusitis (ICARS) examined the evidence for antibiotic use in CRS with and without nasal polyps in depth [1]. The consensus statement makes note of the “surprising paucity of evidence in the literature” and was unable to make any recommendation for use of nonmacrolide antibiotics in nonpolypoid CRS due to a “lack of rigorous clinical studies.” In CRS with nasal polyps, there was a recommendation against the use of nonmacrolide antibiotics given a lack of evidence for efficacy outside of acute exacerbations, and potential for harm. This is consistent with findings from our study, where polyp patients used less oral antibiotics than their nonpolyp counterparts. Macrolide antibiotics were considered separately in ICARS due to their anti-inflammatory properties, and are considered an “option” in CRS with polyps based on limited data demonstrating

reduction in polyp burden and symptoms, particularly in the postoperative setting. The use of “broad-spectrum” antibiotics as part of the paradigm should also be reconsidered, as use of broad-spectrum agents has been growing in many conditions where narrow-spectrum agents may be as effective [53], and carry the potential for more side effects or deleterious microbiome effects. It is clear that complete and well-defined guidelines are needed for antibiotic use in CRS, specifically in regard to (1) when antibiotics should be given, (2) choice of antibiotic, (3) duration of antibiotic administration, (4) method of drug delivery (ie, oral versus topical), and (5) frequency of antibiotic use before consideration of sinus surgery.

There are several limitations of the current study, most notably the challenge of quantifying antibiotic use. We utilized a patient questionnaire to assess this, and as such, recall bias is a potential factor. To limit recall bias we asked patients only about the prior 90 days, although we are interested in a longer time period, of course. Perhaps moving forward, pharmacy or electronic health records database examination of integrated health systems will be an accurate means of assessing antibiotic use. Preoperative antibiotic use (days out of the previous 90) was categorized into approximately quartile groups in order to maximize statistical power. This classification may be a somewhat arbitrary categorization of antibiotic use for CRS patients, as it is currently unknown if there is a potential threshold for untoward effects of antibiotic use after a certain point. In addition to the relationship between patient and provider, antibiotic administration prior to ESS may be driven by third party payors who may demand inappropriate and prolonged antibiotic trials prior to approval for surgical intervention. So, some of decision-making driving antibiotic use in our cohort may have resulted from these external influences. In this study, we do not differentiate antibiotics taken peri-operatively for surgical reasons, and those taken primarily for the disease. However, study enrollment and design naturally limits the inclusion of perioperative antibiotics in the data, as patients were screened and enrolled prior to making the decision for ESS and the mean follow-up assessment at 1.2 years out from surgery. We acknowledge that antibiotic use was assessed at just one or two points in time during a long-term chronic disease treatment process, which does not capture more extended (i.e. lifetime) antibiotic use and its potential effects on QOL and disease severity measures. In addition, the initial PROM appraisal occurred immediately after the antibiotic therapy assessment period, and therefore the overall efficacy of antibiotics in this study group cannot be definitively assessed, as it is possible that antibiotic use did not sufficiently improve symptoms in this cohort. Understanding and defining the effects of the overall amount and historical duration of antibiotic use in CRS will be of interest moving forward, and creating reliable ways to document these measurements will be required. Finally, this study was performed within the academic practices of subspecialty Rhinologists, and consideration must be given to whether results from this study can be generalized to all CRS patients.

CONCLUSION

High-utilization of antibiotics was observed in a multi-institutional cohort of refractory CRS patients electing ESS. Amount of antibiotic use did not correlate with objective measures of disease severity or presence of associated comorbid diseases. Age, polyp status, and patient symptom burden were the main factors correlating with antibiotic use in this CRS

population, signifying that clearer guidelines are required to define appropriate antibiotic use in CRS.

Acknowledgments

Financial Disclosures: V.R.R. serves as a consultant for Medtronic, Inc which is not affiliated with this investigation; T.L.S., Z.M.S., and J.C.M. are supported by a grant for this investigation from the National Institute on Deafness and Other Communication Disorders (NIDCD), one of the National Institutes of Health, Bethesda, MD., USA (R01 DC005805; PI/PD: T.L.S.). Public clinical trial registration (www.clinicaltrials.gov) ID# NCT01332136. This funding organization did not contribute to the design or conduct of this study; preparation, review, approval or decision to submit this manuscript for publication. Z.M.S. is also supported by another grant from the NIDCD (R03 DC013651; PI/PD: Z.M.S.) which is not affiliated with this investigation.

The authors would like to thank Drs. Peter Hwang, MD, and Luke Rudmik, MD, for their contributions in study enrollment.

REFERENCES

1. Orlandi RR, Kingdom TT, Hwang PH, et al. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis. *Int Forum Allergy Rhinol.* 2016; 6(Suppl 1):S22–S209. Section X.B. [PubMed: 26889651]
2. Marple BF, Stankiewicz JA, Baroody FM, et al. Diagnosis and management of chronic rhinosinusitis in adults. *Postgrad Med.* 2009; 121:121–139. [PubMed: 19940423]
3. AAO-HNS. Clinical Indicators: Endoscopic Sinus Surgery, Adult. 2012 [Accessed September 15, 2015] <http://www.entnet.org/Practice/Endoscopic-Sinus-Surgery-Adult.cfm>.
4. Dautremont JF, Rudmik L. When are we operating for chronic rhinosinusitis? A systematic review of maximal medical therapy protocols prior to endoscopic sinus surgery. *Int Forum Allergy Rhinol.* 2015; 5:1095–1103. [PubMed: 26201538]
5. Fokkens WJ, Lund VJ, Mullol J, et al. European position paper on rhinosinusitis and nasal polyps 2012. *Rhinol Suppl.* 2012; 23:1–298.
6. Vangay P, Ward T, Gerber JS, Knights D. Antibiotics, pediatric dysbiosis, and disease. *Cell Host Microbe.* 2015; 17(5):553–564. [PubMed: 25974298]
7. Centers for Disease Control and Prevention. [December 15, 2014] Delivering safe care for patients. 2014 Nov. <http://www.cdc.gov/getsmart/community/materials-references/print-materials/hcp/index.html>
8. Centers for Disease Control and Prevention. [December 15, 2014] Antibiotic resistance: questions and answers. 2015 Apr. <http://www.cdc.gov/getsmart/community/about/antibiotic-resistance-faqs.html>
9. Centers for Disease Control and Prevention. [December 15, 2014] Fast Facts. 2015 Apr. <http://www.cdc.gov/getsmart/antibiotic-use/fast-facts.html>
10. Boucher HW, Talbot GH, Benjamin DK, et al. 10 × '20 Progress--development of new drugs active against gram-negative bacilli: an update from the Infectious Diseases Society of America. *Clin Infect Dis.* 2013; 56(12):1685–1694. [PubMed: 23599308]
11. Rosenfeld RM, Andes D, Bhattacharyya N, et al. Clinical practice guideline: adult sinusitis. *Otolaryngol Head Neck Surg.* 2007; 137(3):365–377. [PubMed: 17765760]
12. Alt JA, Smith TL, Schlosser RJ, et al. Sleep and quality of life improvements after endoscopic sinus surgery in chronic rhinosinusitis. *Int Forum Allergy Rhinol.* 2014; 4(9):693–701. [PubMed: 25079334]
13. DeConde AS, Mace JC, Alt JA, et al. Longitudinal improvement and stability of the SNOT-22 survey in the evaluation of surgical management for chronic rhinosinusitis. *Int Forum Allergy Rhinol.* 2015; 5(3):233–239. [PubMed: 25511442]
14. Alt JA, DeConde AS, Mace JC, et al. Quality of life in patients with chronic rhinosinusitis and sleep dysfunction undergoing endoscopic sinus surgery: A pilot investigation of comorbid obstructive sleep apnea. *JAMA Otolaryngol Head Neck Surg.* 2015; 141(10):873–881. [PubMed: 26356240]

15. Soler ZM, Smith TL, Alt JA, et al. Olfactory-specific quality of life outcomes after endoscopic sinus surgery. *Int Forum Allergy Rhinol.* 6(4):407–413. [PubMed: 26678351]
16. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, Brook I, et al. Clinical practice guideline (update): adult sinusitis. *Otolaryngol Head Neck Surg.* 2015; 152(2 Suppl):S1–S39.
17. Lund VJ, Kennedy DW. Quantification for staging sinusitis. The Staging and Therapy Group. *Ann Otol Rhinol Laryngol Suppl.* 1995; 167:17–21. [PubMed: 7574265]
18. Lund VJ and Mackay IS. Staging in rhinosinusitis. *Rhinology.* 1992; 31(4):183–184.
19. Doty RL, Marcus A, Lee WW. Development of the 12-item cross-cultural smell identification test (CC-SIT). *Laryngoscope.* 1996; 106:353–356. [PubMed: 8614203]
20. El Rassi E, Mace JC, Steele TO, et al. Sensitivity analysis and diagnostic accuracy of the Brief Smell Identification Test in patients with rhinosinusitis. *Int Forum Allergy Rhinol.* 2016; 6(3):287–292. [PubMed: 26625169]
21. Piccirillo JF, Merritt MG Jr, Richards ML. Psychometric and clinimetric validity of the 20-Item Sino-Nasal Outcome Test (SNOT-20). *Otolaryngol Head Neck Surg.* 2002; 126(1):41–47. [PubMed: 11821764]
22. Hopkins C, Gillett S, Slack R, et al. Psychometric validity of the 22-item Sinonasal Outcome Test. *Clin Otolaryngol.* 2009; 34(5):447–454. [PubMed: 19793277]
23. DeConde AS, Mace JC, Bodner T, et al. SNOT-22 quality of life domains differentially predict treatment modality selection in chronic rhinosinusitis. *Int Forum Allergy Rhinol.* 2014; 4(12):972–979. [PubMed: 25323055]
24. Senior BA, Glaze C, Benninger MS. Use of the rhinosinusitis disability index (RSDI) in rhinologic disease. *Am J Rhinol.* 2001; 15(1):15–20. [PubMed: 11258649]
25. Head K, Chong LY, Piromchai P, et al. Systemic and topical antibiotics for chronic rhinosinusitis. *Cochrane Database Syst Rev.* 2016 Apr 26;4:CD011994. [PubMed: 27113482]
26. Soler ZM, Oyer SL, Kern RC, et al. Antimicrobials and chronic rhinosinusitis with or without polyposis in adults: an evidenced-based review with recommendations. *Int Forum Allergy Rhinol.* 2013 Jan; 3(1):31–47. [PubMed: 22736403]
27. Bhandarkar ND, Mace JC, Smith TL. Endoscopic sinus surgery reduces antibiotic utilization in rhinosinusitis. *Int Forum Allergy Rhinol.* 2011; 1(1):18–22. [PubMed: 21666846]
28. Gliklich RE, Metson R. Economic implications of chronic sinusitis. *Otolaryngol Head Neck Surg.* 1998; 118(3 Pt 1):344–349. [PubMed: 9527115]
29. Smith TL, Mendolia-Loffredo S, Loehrl TA, et al. Predictive factors and outcomes in endoscopic sinus surgery for chronic rhinosinusitis. *Laryngoscope.* 2005; 115(12):2199–2205. [PubMed: 16369166]
30. Benninger MS, Holy CE. The impact of endoscopic sinus surgery on health care use in patients with respiratory comorbidities. *Otolaryngol Head Neck Surg.* 2014; 151(3):508–515. [PubMed: 24894312]
31. Vashista R, Soler ZM, Nguyen SA, Schlosser RJ. A systematic review and meta-analysis of asthma outcomes following endoscopic sinus surgery for chronic rhinosinusitis. *Int Forum Allergy Rhinol.* 2013; 3(10):788–794. [PubMed: 23818462]
32. Soler ZM, Mace J, Smith TL. Fibromyalgia and chronic rhinosinusitis: outcomes after endoscopic sinus surgery. *Am J Rhinol.* 2008; 22(4):427–432. [PubMed: 18702911]
33. Hajjij A, Mace JC, Soler ZM, et al. The impact of diabetes mellitus on outcomes of endoscopic sinus surgery: a nested case-control study. *Int Forum Allergy Rhinol.* 2015; 5(6):533–540. [PubMed: 25913815]
34. Orb Q, Mace JC, Deconde AS, et al. Patients electing medical vs surgical treatment: emotional domain of the Rhinosinusitis Disability Index associates with treatment selection. *Int Forum Allergy Rhinol.* 2016; 6(3):315–321. [PubMed: 26536520]
35. Smith SS, Evans CT, Tan BK, et al. National burden of antibiotic use for adult rhinosinusitis. *J Allergy Clin Immunol.* 2013 Nov; 132(5):1230–1232. [PubMed: 23987794]
36. Kingdom TT, Swain RE Jr. The microbiology and antimicrobial resistance patterns in chronic rhinosinusitis. *Am J Otolaryngol.* 2004 Sep-Oct;25(5):323–328. [PubMed: 15334396]

37. Bhattacharyya N, Kepnes LJ. Assessment of trends in antimicrobial resistance in chronic rhinosinusitis. *Ann Otol Rhinol Laryngol*. 2008 Jun; 117(6):448–452. [PubMed: 18646442]
38. Rickert SM, Rachakonda T, Hiltzik DH, Kacker A. Microbiology and antibiotic resistance of chronic rhinosinusitis in patients undergoing primary vs. revision endoscopic sinus surgery. *Laryngoscope*. 2010; 120(Suppl 4):S243. [PubMed: 21225841]
39. Jokinen K, Raunio V. Penetration of azidocillin into the secretion and tissues in chronic maxillary sinusitis and tonsillitis. *Acta Otolaryngol*. 1975; 79(5–6):460–465. [PubMed: 1174004]
40. Karma P, Pukander J, Penttilä M. Azithromycin concentrations in sinus fluid and mucosa after oral administration. *Eur J Clin Microbiol Infect Dis*. 1991; 10(10):856–859. [PubMed: 1662632]
41. Dinis PB, Monteiro MC, Martins ML, et al. Sinus tissue pharmacokinetics after oral administration of amoxicillin/clavulanic acid. *Laryngoscope*. 2000; 110(6):1050–1055. [PubMed: 10852529]
42. Andersson DI, Hughes D. Microbiological effects of sublethal levels of antibiotics. *Nat Rev Microbiol*. 2014; 12:465–478. [PubMed: 24861036]
43. Kohanski MA, Tharakan A, Lane AP, Ramanathan M Jr. Bactericidal antibiotics promote reactive oxygen species formation and inflammation in human sinonasal epithelial cells. *Int Forum Allergy Rhinol*. 2016 Feb; 6(2):191–200. [PubMed: 26624249]
44. Biedermann L, Rogler G. The intestinal microbiota: its role in health and disease. *Eur J Pediatr*. 2015; 174(2):151–167. [PubMed: 25563215]
45. Droste JH, Wieringa MH, Weyler JJ, et al. Does the use of antibiotics in early childhood increase the risk of asthma and allergic disease? *Clin Exp Allergy*. 2000; 30:1547–1553. [PubMed: 11069562]
46. Johnson CC, Ownby DR, Alford SH, et al. Antibiotic exposure in early infancy and risk for childhood atopy. *J Allergy Clin Immunol*. 2005; 115:1218–1224. [PubMed: 15940137]
47. Ong MS, Umetsu DT, Mandl KD. Consequences of antibiotics and infections in infancy: bugs, drugs, and wheezing. *Ann Allergy Asthma Immunol*. 2014; 112:441–445. [PubMed: 24631182]
48. Russell SL, Gold MJ, Hartmann M, et al. Early life antibiotic-driven changes in microbiota enhance susceptibility to allergic asthma. *EMBO Rep*. 2012; 13:440–447. [PubMed: 22422004]
49. Stefka AT, Feehley T, Tripathi P, et al. Commensal bacteria protect against food allergen sensitization. *Proc Natl Acad Sci USA*. 2014; 111:13145–13150. [PubMed: 25157157]
50. Faith JJ, Guruge JL, Charobonneau M, et al. The long-term stability of the human gut microbiota. *Science*. 2013; 341(6141):1237439. [PubMed: 23828941]
51. Claesson MJ, Cusack S, O'Sullivan O, et al. Composition, variability, and temporal stability of the intestinal microbiota of the elderly. *Proc Natl Acad Sci USA*. 2011; 108(Suppl 1):4586–4591. [PubMed: 20571116]
52. Vickery TW, Ramakrishnan VR. Bacterial pathogens and the microbiome. *Otolaryngol Clin N Am*. 2016 In press.
53. Hersh AL, Jackson MA, Hicks LA. American Academy of Pediatrics Committee on Infectious Diseases. Principles of judicious antibiotic prescribing for upper respiratory tract infections in pediatrics. *Pediatrics*. 2013; 132:1146–1154. [PubMed: 24249823]

Table 1

Demographics and comorbid disease characteristics stratified across preoperative antibiotic use (days out of previous 90 before ESS) groups (n=434)

Cofactors:	0 Days Antibiotics (n= 163)	1–14 Days Antibiotics (n=102)	15–28 Days Antibiotics (n=69)	29+ Days Antibiotics (n=100)	p-value
Antibiotic use (days) Mean[SD]	0.0[–]	9.9[3.6]	21.1[3.3]	50.7[22.2]	<0.001
Follow-up (mo.) Mean[SD]	14.7[5.2]	15.1[5.3]	14.5[5.4]	15.0[4.8]	0.862
Age (years) Mean[SD]	52.2[15.7]	47.2[14.7]	48.6[15.4]	54.5[14.8]	0.003
Males n(%)	89(55%)	40 (39%)	29 (42%)	44 (44%)	0.063
White / Caucasian n(%)	141 (87%)	87 (85%)	57 (83%)	88 (88%)	0.794
Hispanic / Latino n(%)	10 (6%)	6 (6%)	3 (4%)	7 (7%)	0.915
Smoking history n(%)	4 (3%)	6 (6%)	3 (4%)	7 (7%)	0.341
Allergies n(%)	75 (46%)	47 (46%)	30 (44%)	44 (44%)	0.975
CRSwNP n(%)	77 (47%)	36 (35%)	20 (29%)	22 (22%)	<0.001
Asthma n(%)	60 (37%)	33 (32%)	26 (38%)	45 (45%)	0.313
ASA sensitivity n(%)	17 (10%)	8 (8%)	3 (4%)	6 (6%)	0.369
Fibromyalgia n(%)	4 (3%)	4 (4%)	4 (6%)	7 (7%)	0.325
Depression n(%)	23 (14%)	15 (15%)	10 (15%)	17 (17%)	0.933
Previous ESS n(%)	83 (51%)	45 (44%)	38 (55%)	61 (61%)	0.106
DM – Type I/II n(%)	13 (8%)	6 (6%)	3 (4%)	9 (9%)	0.626
Steroid dependency n(%)	12 (7%)	7 (7%)	2 (3%)	14 (14%)	0.056
Septal deviation n(%)	76 (47%)	42 (41%)	30 (44%)	33 (33%)	0.184

SD, standard deviation; CRSwNP, chronic rhinosinusitis with nasal polyps; ASA, acetylsalicylic acid; ESS, endoscopic sinus surgery; DM, diabetes mellitus. P-values represent significant difference between at least 2 antibiotic use categories using omnibus testing - either analysis of variance (ANOVA) for continuous factors or chi-square (χ^2) 4x2 contingency tables.

Table 2

Frequency of unilateral and bilateral ESS interventional procedures stratified across preoperative antibiotic use (days out of previous 90 before ESS) groups (n=434)

Procedure type:	0 Days Antibiotics (n= 163)	1-14 Days Antibiotics (n=102)	15-28 Days Antibiotics (n=69)	29+ Days Antibiotics (n= 100)	p-value
Maxillary antrostomy n(%)	154 (95%)	100 (98%)	66 (96%)	95 (95%)	0.567
Partial ethmoidectomy n(%)	27 (17%)	22 (22%)	15 (22%)	16 (16%)	0.585
Total ethmoidectomy n(%)	130 (80%)	81 (79%)	49 (71%)	79 (79%)	0.487
Sphenoidotomy n(%)	118 (72%)	69 (68%)	47 (68%)	69 (69%)	0.833
Middle turbinate resection n(%)	27 (17%)	10 (10%)	14 (20%)	14 (14%)	0.254
Inferior turbinate reduction n(%)	39 (24%)	21 (21%)	18 (26%)	16 (16%)	0.355
Septoplasty n(%)	80 (49%)	46 (45%)	27 (39%)	34 (34%)	0.095
Frontal sinusotomy Draf I n(%)	14 (9%)	8 (8%)	7 (10%)	10 (10%)	0.933
Frontal sinusotomy Draf IIa n(%)	85 (52%)	57 (56%)	34 (49%)	43 (43%)	0.302
Frontal sinusotomy Draf IIb n(%)	10 (6%)	5 (5%)	8 (12%)	11 (11%)	0.203
Frontal sinusotomy Draf III n(%)	1 (1%)	3 (3%)	0 (0%)	7 (7%)	0.006
Image guidance n(%)	108 (66%)	68 (67%)	44 (64%)	73 (73%)	0.580

P-values represent significant difference between at least 2 antibiotic use categories using omnibus chi-square (χ^2) testing and 4x2 contingency tables.

Table 3

Average preoperative clinical measures of disease severity and PROM scores stratified across preoperative antibiotic use (days out of previous 90 before ESS) groups (n=434)

Preoperative PROM:	0 Days Antibiotics (n=163)	1–14 Days Antibiotics (n=102)	15–28 Days Antibiotics (n=69)	29+ Days Antibiotics (n=100)	p-value
	Mean[SD]	Mean[SD]	Mean[SD]	Mean[SD]	
SNOT-22 total score	49.5[20.0]	54.9[18.6]	56.2[18.0]	55.8[21.3]	0.030
Rhinologic symptom domain	16.6[6.5]	17.2[5.9]	16.6[6.6]	15.7[6.3]	0.393
Extra-nasal rhinologic domain	7.8[3.7]	9.1[3.1]	8.8[3.3]	8.9[3.8]	0.013
Ear / facial symptom domain	8.4[5.2]	10.2[4.8]	9.7[4.8]	9.7[5.6]	0.019
Psychological dysfunction domain	14.3[8.1]	16.0[7.8]	17.2[7.6]	18.0[8.8]	0.002
Sleep dysfunction domain	12.5[6.6]	13.6[6.9]	15.1[6.3]	14.9[6.5]	0.006
RSDI total score	39.5[23.5]	46.8[21.3]	53.7[23.3]	52.6[26.3]	<0.001
Physical domain	16.9[9.0]	18.9[8.2]	20.8[8.8]	20.4[9.8]	0.003
Functional domain	12.1[8.5]	15.2[7.5]	18.0[8.1]	17.5[9.1]	<0.001
Emotional domain	10.4[8.2]	12.7[8.0]	14.9[8.7]	14.7[9.7]	<0.001
Clinical Measure of Disease Severity					
Endoscopy scores	6.3[4.0]	6.0[3.8]	5.6[3.8]	5.3[3.6]	0.326
CT scores	11.9[6.8]	12.2[6.1]	10.9[6.2]	10.9[5.9]	0.357
BSIT scores	8.5[3.3]	8.8[3.1]	9.4[2.6]	9.0[2.9]	0.480

PROM, patient-reported outcome measure; SD, standard deviation; SNOT-22, 22-item SinoNasal Outcome Test; RSDI, Rhinosinusitis Disability Index; CT, computed tomography; BSIT, Brief Snell Identification Test. P-values represent significant difference between at least 2 antibiotic use categories using either ANOVA or Kruskal-Wallis omnibus testing, depending on data distribution. Significant findings after adjustment for multiple comparisons are discussed in the text.

Average within-subject improvements in reported mean antibiotic use days (out of previous 90 days) stratified across preoperative antibiotic use groups

Table 4

Preoperative Antibiotic Use:	Pre-ESS Antibiotic Days		Post-ESS Antibiotic Days		t-statistic	p-value
	Mean [SD]	Range	Mean [SD]	Range		
0 Days (n=159)	0.0 [---]	n/a	4.8 [14.8]	[0–90]	–4.09	<0.001
1–14 Days (n=100)	9.9 [3.6]	[1–14]	4.7 [12.3]	[0–90]	4.03	<0.001
15–28 Days (n=69)	21.1 [3.3]	[15–28]	7.4 [18.1]	[0–90]	6.33	<0.001
29+ Days (n=99)	50.7 [22.2]	[29–90]	12.0 [21.7]	[0–90]	12.91	<0.001

SD, standard deviation. P-values represent significant difference for the paired samples t-test statistic to evaluate mean improvement over time.