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Is greater antibiotic therapy prior to ESS associated with differences in surgical outcomes in CRS?

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Abstract

Objective—Antibiotics have been a mainstay of CRS therapy, however, data suggest that antibiotics may also result in several adverse unintended consequences. We aimed to evaluate if greater antibiotic use prior to sinus surgery was associated with differences in surgical outcomes.

Methods—Adult CRS patients enrolled in a prospective, multi-institutional, observational cohort study were asked to recall systemic antibiotic use in the 90 days prior to ESS. Antibiotic use was examined in relation to demographics, disease characteristics, and outcomes.

Results—Data were collected for 271 study participants followed for a mean of 14.9 [± 5.1] months across 4 institutions, with a mean preoperative antibiotic use of 27.8 [± 22.7] days out of the 90 preceding ESS. After ESS, significant improvement ($p < 0.001$) was reported for PROMs and endoscopy scores for the overall cohort. No bivariate correlation between preoperative antibiotic use and degree of benefit in objective clinical measures (endoscopy, BSIT) was seen. Increased preoperative antibiotic use was associated with less improvement in SNOT-22 and its Rhinologic subdomain after ESS. Prevalence of achieving an MCID in overall SNOT-22 symptom scores was lower in those using more preoperative antibiotics, although statistical significance was not reached when adjusting for independent covariates in multivariate modeling.

Conclusion—Higher amounts of previous antibiotic use do not appear to be associated with better ESS outcomes. Specific recommendations for antibiotic use as part of CRS appropriate medical therapy prior to ESS require further study, particularly given concerns for antibiotic overuse and implications for improving outcomes in the modern healthcare era.

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Keywords

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

INTRODUCTION

Antibiotic therapy has been grandfathered in as a mainstay in the medical management of chronic rhinosinusitis (CRS) despite lack of evidence for its efficacy in routine use, or an understanding of specific temporal and disease characteristics to guide appropriateness of administration [1–4]. Current re-examination of antibiotic use in medicine has been spurred by a combination of issues including emergence of drug-resistant organisms, side effects, drug interactions, and cost burden [5–8]. Recognition of antibiotic overuse in many medical disciplines has led to incorporation of evidence-based medicine into recent guidelines curtailing antibiotic therapies to only the most appropriate of scenarios. The high prevalence of CRS, combined with the frequent use of antibiotics as part of its medical therapy, has resulted in this disease accounting for an astounding degree of antibiotic use. One study analyzing the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey Outpatient Department Data from 2006–2010 found that CRS was responsible for 7.1% of antibiotic visits, more than any other individual diagnosis [9]. Repeated antibiotic administration is often utilized as a method of treatment in refractory CRS until both the patient and physician are comfortable moving forward to surgical intervention, and in this transition there is a lack of clarity into the optimal timing for progression to surgical intervention.

Guidelines and evidence-based consensus statements [1,2] have presented antibiotic use as an “*option*” for therapy left to the provider’s discretion. However, in many medical systems antibiotics are required to some degree prior to advancing a patient with CRS to endoscopic sinus surgery (ESS). Much research has been done in recent years to examine why patients eventually move on from medical therapies to elective ESS, but little is known about the effects of the repeated antibiotic therapies they undergo during the initial medical management phase of the disease. Beyond antibiotic-associated concerns mentioned above, newer concepts surrounding the “negative effects” of antibiotic use have been gaining attention, particularly as microbiome research continues to evolve. Novel discoveries correlating frequent antibiotic use with subsequent development of allergies and asthma have been observed in children, and are posited to result from microbiome disturbances [10,11]. Although these studies have not yet been expanded to the adult population, the broader implications are intriguing. The current discourse on whether repeated courses of antibiotics are required prior to transitioning to surgical therapy sets the underlying context for this investigation.

Given the potential for negative local and general health effects resulting from frequent antibiotic use prior to ESS, we aimed to examine the possible effect of antibiotic exposure on outcomes of subsequent treatment, i.e. ESS.

MATERIALS and METHODS

Heterogeneous Study Population and Inclusion Criteria

Adult patients (≥ 18 years old) were recruited into a prospective, multi-center, observational cohort study designed to evaluate treatment outcomes of endoscopic sinus surgery (ESS), for which multiple reports have been previously published [12–16]. Study patients included those with medically refractory CRS as defined by both the American Academy of Otolaryngology-Head and Neck Surgery 2007 guidelines [17] and the European Position Paper on Rhinosinusitis and Nasal Polyps 2012 [2], and had taken at least one course of antibiotics for CRS in the 90 days prior to enrollment. The Institutional Review Boards (IRBs) at each performance site presided over study protocols, informed consent documents, and data safety monitoring. Performance sites consisted of sinus centers located within tertiary care academic hospital systems 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 elected ESS as the subsequent treatment option for symptom relief related to CRS after prior 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. Broad-spectrum antimicrobials were defined as agents with expected efficacy against both gram-positive and gram-negative bacteria, with anticipated coverage of multiple respiratory pathogens (eg, beta-lactamase inhibiting penicillins, respiratory fluoroquinolones, tetracyclines, macrolides, second- to fourth-generation cephalosporins, trimethoprim/sulfamethoxazole) [18,19]. Study enrollment occurred after participants elected ESS, during which they were screened for demographics, social and medical history including factors outlined in Table 1. Diagnoses of asthma, allergy, and aspirin sensitivity were made by presence of classic symptoms and self-report of prior testing. Participants were followed postoperatively through standard of care clinic visits for up to 18-months and asked to complete postoperative study evaluations at 6-month intervals, either during clinic appointments or follow-up study mailings.

Endoscopic Sinus Surgery

The degree of surgical intervention performed was determined by the discretion of each enrolling surgeon. Study participants included both primary and revision ESS cases, and procedures included unilateral or bilateral maxillary antrostomy, partial or total 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 was used selectively according to AAO-HNS indications and surgeon discretion. Postoperative medical therapies were prescribed as needed but, at a minimum, included 240ml of daily low-pressure nasal saline irrigation to promote optimal postoperative healing [3].

Exclusion Criteria

Participants were considered lost to follow-up if no postoperative evaluations were provided between 6 and 18 months after the date of ESS. Subjects with 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

Sinonasal endoscopy exams were completed with a 0–30° rigid endoscope and staged by each enrolling physician using the Lund-Kennedy endoscopy scoring system [20]. Study participants also provided high-resolution computed tomography (CT) radiographic imaging of the paranasal sinuses preoperatively, where each enrolling physician reviewed images and staged each scan using the Lund-Mackay scoring system [21]. Olfactory function and detection was measured during each study evaluation time point using the Brief Smell Identification Test (BSIT) (Sensonics Inc., Haddon Heights, NJ.), where higher BSIT total scores (score range: 0–12) reflect a better sense of smell [22,23].

Patient Reported Outcome Measures

The first patient reported outcome measure (PROM) 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) [24,25]. 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) [26].

The second utilized PROM was the Rhinosinusitis Disability Index (RSDI), a 30-item survey developed to quantify symptom severity associated with CRS in a complementary 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 [27]. The enrolling physician/surgeon was blinded to survey responses for the entire study duration.

Prescribed Systemic Antibiotic Use

Study participants were asked to recall medication use for treatment of their CRS-related symptoms. As the primary exposure variable of interest in this study, participants reported the number of days out of the previous 90 days that systemic antibiotics were taken for sinus-related indications.

Data Management and Statistical Analyses

Protected health information was removed and study data were safeguarded using unique study identification number assignment for participants. 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 SPSS (IBM Corporation, Armonk, NY.). Study data were evaluated descriptively, and

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 tertiles to maximize statistical power and sensitivity between independent groups. 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. Further evaluation of PROMs was conducted using simple stepwise linear regression to adjust for significant cofactors across antibiotic use groups. Final regression models were constructed using manual forward selection ($p < 0.100$) and backwards elimination ($p < 0.050$) of all screened cofactors. Confounding was identified 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 271 study participants met all criteria and were prospectively enrolled between April 2011 and July 2015. Study participants with follow-up reported an average of 27.8 [± 22.7] days of preoperative antibiotic use [median 21.0 days] out of the prior 90 days at enrollment. Demographics and disease characteristics, stratified across antibiotic use groups, are outlined in Table 1 and the prevalence of ESS procedures performed are described in Supplemental Table 1. The mean age for the overall cohort was 50.3 [± 15.2] years with a median of 52.0 years. Significant, unadjusted within-subject improvement in both PROMs and objective measures of disease were noted for the overall cohort, consistent with numerous prior reports. For the overall cohort, SNOT-22 and RSDI improved by 25.9 [± 22.0] points and 24.1 [± 23.3] points, respectively (both $p < 0.001$); mean endoscopy scores significantly improved by 3.2 [± 3.9] points ($p < 0.001$), however, BSIT scores did not significantly differ ($p = 0.62$) postoperatively with a mean difference of 0.1 [± 2.8] points.

Study participants reporting 1–14 days of antibiotic use prior to surgery were younger in age than participants reporting 29+ days of preoperative antibiotic use ($p = 0.002$) after adjustment for multiple comparisons. Differences in the prevalence of respiratory comorbidities (allergies, asthma, and aspirin sensitivity) were not associated with increased preoperative antibiotic use groups, neither were comorbid diagnoses of fibromyalgia, depression, or diabetes. Study participants reporting more than 29 days of preoperative antibiotics were associated with a significantly higher unadjusted prevalence of corticosteroid dependency, compared to patient groups reporting less antibiotic use. Draf III frontal sinusotomy procedures were infrequently performed, however, patients undergoing this degree of frontal operation were more likely to have had greater antibiotic use ($p = 0.053$). Neither subjective nor objective disease severity measures were associated with increased antibiotic use.

Antibiotics, PROMs, and objective measures of disease

Study participants were initially stratified by antibiotic use in the prior 90 days into three categories as has been done in previous a report on this cohort [16]: low (1–14 days),

medium (15–28 days), and high (29+ days). Mean degree of postoperative improvement in total SNOT-22 score and the Rhinologic symptom domain was statistically less in the high antibiotic use group (Table 2), as were the frequencies of achieving a minimal clinically important difference (MCID) in these outcomes measures (Table 3). Preoperative antibiotic use was not associated with postoperative outcomes in other SNOT-22 domains, RSDI or its individual domains, or objective disease measures such as endoscopy or BSIT scores.

In examining these findings further, a regular “dose-dependent” association pattern between antibiotic use groups and outcomes is not observed, as only the highest antibiotic users exhibit any statistical decrease in outcome gains. Unadjusted linear regression analysis between preoperative antibiotic use and degree of improvement in clinical measures of disease severity and PROM scores was performed, and is described in Table 4. Increased antibiotic use did not correlate with degree of improvement in endoscopy or BSIT scores, but had a weak negative correlation with degree of improvement in the SNOT-22 Rhinologic symptom domain, indicating that more antibiotic use was associated with less symptomatic improvement. In terms of achieving an MCID in outcome variables according to antibiotic use, high use of preoperative antibiotics demonstrated a decreased likelihood of achieving an MCID in overall SNOT-22 and several subdomains (Table 3). Specifically, high antibiotic users (29+ days out of prior 90) were less likely to achieve an MCID in overall SNOT-22 and the Rhinologic, Extra-nasal, and Ear/Facial subdomains after ESS. Twenty-seven separate cofactors were screened for univariate significance, and significant covariates were applied in an adjusted, multivariate model to evaluate the significant associations seen in Supplementary Table 2. Statistical significance of MCID associations with antibiotic use were eliminated after adjusting for these multiple covariates (e.g. age, nasal polyposis, revision surgery, preoperative endoscopy score severity; Table 5). No significant interaction or confounding effects were identified using either multivariate modeling approach.

Institutional Differences of Antibiotic Use

Preoperative antibiotic administration was compared across institutions, as has been done in prior reports from this study cohort. Patient enrollees and surgeons came from tertiary care specialty Rhinology practices with providers well-versed in current guidelines for antibiotic use and with extensive experience in ESS. Average preoperative antibiotic use days ranged from 21.5 [± 19.9] to 31.5 [± 23.0] days between enrollment sites and no significant differences in average antibiotic use days between any enrollment sites was noted ($F_{(2)}=1.20$; $p=0.311$)

DISCUSSION

The heterogeneous group of patients diagnosed with CRS, coupled with incomplete understanding of the pathophysiology of medically-refractory CRS, has resulted in a paradigm of unclear repeated medical therapies until either the patient or the physician are ready to move on to surgical intervention. We previously reported that CRS patients who use the most antibiotics tended to be older patients, those with nonpolypoid CRS, and those with the worst symptom burden, irrespective of comorbidities or objective measurements of their disease severity [16]. In the same study, we reported that antibiotic use decreased by 60%

across all groups after ESS at >6 month follow-up. In the current study, we observed that refractory CRS patients undergoing ESS all tended to improve by the same degree regardless of preoperative antibiotic use. In fact, there may even be a small negative association between high preoperative antibiotic use if we were underpowered to make the statistical observation. The incorporation of these associations into existing data demonstrating that continued medical therapy (CMT) does not offer continued benefit when refractory CRS patients are candidates for ESS [28,29], suggests that the point at which practitioners transition from CMT to consideration of ESS requires more attention. Certainly, it would be ideal to predict which patients are unlikely to benefit from CMT and move them to ESS quicker, as has been proposed by others for various reasons including value-based healthcare concerns and potential for limiting development of respiratory comorbidities [30–33].

The decision for progression from medical therapy to ESS in CRS patients has been observationally studied, and it appears that non-Rhinologic symptom burden is one of the main drivers for patients to elect ESS rather than CMT [34–36]. With an unclear physician's algorithm for when to declare failure of CMT and progression to ESS, and lack of specifics regarding utility of antibiotics in CRS, it is no surprise that repeated use of antibiotics occurs in these cases. Our data indicate that repeated or prolonged use of systemic antibiotics in those destined for ESS is not likely to improve disease outcomes after intervention, and suggest there may even be a subtle detriment to their ongoing use. However, there are some patients who may benefit from prolonged antibiotic therapy—particularly macrolides—and may use this to avoid procedural intervention. The ability to stratify CRS patients and predict therapeutic outcomes would be helpful for this dilemma. Beyond the much-publicized concerns for development of antibiotic resistance, repeated antibiotic exposure may be counterproductive to the goal of restoration of sinus health. Novel research has demonstrated that antibiotic exposure can increase bacterial pathogenicity through production of pro-inflammatory cytokines, induction of virulence gene transcription, and selecting for persistence of drug resistant organisms [37,38]. Theoretical concerns regarding antibiotic collateral damage on the microbiome also abound, whereby repeated antibiotic exposure may result in unfavorable unintended consequences on the resident microbiome, decreasing occupancy by healthy commensal organisms and reducing diversity. In support of this, a recent case-control study of 1,162 patients reported that general antibiotic exposure (ie, for non-sinus indication) is a significant risk factor for subsequent development of CRS (OR=2.2) and associated with worse CRS-related quality of life [39]. In this study, the class of antibiotic or reason for administration was not a factor in CRS development or CRS-related quality of life.

We are well aware of the high prevalence of CRS and the degree of antibiotics utilized by this population, and are now recognizing that in refractory CRS patients bound for ESS, continued antibiotic use does not offer much likelihood for disease resolution. This recognition that we may need to reconsider when it is most appropriate to move refractory CRS patients out of the continued medical therapy (CMT) phase of treatment on to ESS represents a large opportunity for our specialty. The judicious use of antibiotics is an important public health initiative, and has been recognized as one of four key strategies required to stem the growing problem of antibiotic resistance [40]. Implementation of hospital-based Antibiotic Stewardship Programs have improved patient care, improved

patient safety, reduced treatment failures, reduced hospital infections, and reduced antibiotic resistance, all while saving hospitals money. As a result of these observations, many groups have recommended more widespread implementation of Antibiotic Stewardship Programs, including the Infectious Disease Society of America, CDC, American Society of Health System Pharmacists, and The Joint Commission [41–44]. The themes promoted by such programs are naturally occurring with recent goals in value-based healthcare, such as tracking and reporting of data, and accountability for outcomes. The requisite next steps are education of clinicians about optimal prescribing guidelines and leadership commitment to provide formal recommendations, support training and education in them, and ensure participation from groups of stakeholders. Utilizing data such as those offered in the current study may help inform such decisions for individual clinicians and possibly creation of more formal recommendations.

There are some limitations of the current study that should be addressed, the first is the difficulty in quantifying antibiotic use. Here, a patient questionnaire was utilized and the time period of assessment was limited to a period of 90 days to minimize recall bias. A recent study compared CRS patients' recall of medication usage over the previous 3-month and 12-month periods, noting significant correlation between the two and concluding that the 3-month interval for antibiotic use reporting appeared to be the more clinically relevant time frame for assessing CRS-related quality of life [45]. For the current study hypothesis, an even longer period of time prior to ESS would be ideal to assess, and perhaps this can be achieved in the future using electronic health records or system wide databases. ESS outcomes depend on numerous factors, and it may be difficult to design the ideal study to evaluate long-term causal effects of a single repeated intervention such as antibiotic use. In the current study, multivariate analysis adjusted for significant covariates, but it is still challenging to account for treatment individuality and patient-reported outcomes of severe CRS where antibiotics are often used for any number of underlying disease reasons. The potential for selection bias is present, as we did not have access to sinus culture and antibiotic resistance data, and it is conceivable that patients who present with more severe CRS might be those who are administered more antibiotics. Notably, in a prior analysis of this cohort, this was not the case—objective markers of disease severity such as CT score, endoscopy score, and extent of surgery were not associated with higher antibiotic use [16]. Here, again, we did not note differences in objective disease or CRS-related quality of life measures by antibiotic use at the time of enrollment. In the current study steroid dependency was associated with high antibiotic use, however, on its own steroid dependency was not an independent risk factor or confounding factor in the relationship between antibiotic use and outcomes. Lastly, patients recruited into this study were treated within academic practices of subspecialty Rhinologists, and were a predominantly White/Caucasian ethnicity. As such, applicability of these results to general CRS patients in the community setting should be considered.

CONCLUSION

High-utilization of antibiotics is frequently observed in refractory CRS patients electing ESS, but do not appear to confer any benefit on surgical outcomes in patients proceeding to ESS after medical therapies. Specific recommendations for antibiotic use as part of CRS

appropriate medical therapy prior to ESS require further attention, particularly given concerns for antibiotic overuse and implications for improving outcomes in the modern healthcare era.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.**Study population.**

Demographics and comorbid disease characteristics stratified across preoperative antibiotic use (days out of previous 90 before ESS) groups (n=271)

Independent Cofactors:		1–14 Days Antibiotics (n=102)	15–28 Days Antibiotics (n=69)	29+ Days Antibiotics (n=100)	p-value
Antibiotic use (days)	Mean[±SD]	9.9 [±3.6]	21.1 [±3.3]	50.7 [±22.2]	<0.001
Follow-up (mo.)	Mean[±SD]	15.1 [±5.3]	14.5 [±5.4]	15.0 [±4.8]	0.733
Age (years)	Mean[±SD]	47.2 [±14.7]	48.6 [±15.4]	54.5 [±14.8]	0.002
Males	n(%)	40 (39%)	29 (42%)	44 (44%)	0.787
White / Caucasian	n(%)	87 (86%)	57 (83%)	88 (88%)	0.610
African American	n(%)	4 (4%)	2 (3%)	5 (5%)	0.790
Asian	n(%)	5 (5%)	2 (3%)	3 (3%)	0.713
Other race(s)	n(%)	4 (4%)	8 (12%)	4 (4%)	0.067
Hispanic / Latino ethnicity	n(%)	6 (6%)	3 (4%)	7 (7%)	0.772
Smoking history	n(%)	6 (6%)	3 (4%)	7 (7%)	0.773
Allergies	n(%)	47 (46%)	30 (44%)	44 (44%)	0.933
CRSwNP	n(%)	36 (35%)	20 (29%)	22 (22%)	0.113
Asthma	n(%)	33 (32%)	26 (38%)	45 (45%)	0.180
ASA sensitivity	n(%)	8 (8%)	3 (4%)	6 (6%)	0.646
Fibromyalgia	n(%)	4 (4%)	4 (6%)	7 (7%)	0.629
Depression	n(%)	15 (15%)	10 (15%)	17 (17%)	0.872
Previous ESS	n(%)	45 (44%)	38 (55%)	61 (61%)	0.052
DM – Type I/II	n(%)	6 (6%)	3 (4%)	9 (9%)	0.454
Steroid dependency	n(%)	7 (7%)	2 (3%)	14 (14%)	0.030
Septal deviation	n(%)	42 (41%)	30 (44%)	33 (33%)	0.317
SNOT-22	Mean[±SD]	54.9 [±18.6]	56.2 [±18.0]	55.8 [±21.3]	0.904
RSDI	Mean[±SD]	46.8 [±21.3]	53.7 [±23.3]	52.6 [±26.3]	0.107
Endoscopy Score	Mean[±SD]	6.0 [±3.8]	5.6 [±3.8]	5.3 [±3.6]	0.411
BSIT Score	Mean[±SD]	8.8 [±3.1]	9.4 [±2.6]	9.0 [±2.9]	0.553
CT Score	Mean[±SD]	12.2 [±6.1]	10.9 [±6.2]	10.9 [±5.9]	0.243

SD, standard deviation; CRSwNP, chronic rhinosinusitis with nasal polyposis; ASA, acetylsalicylic acid; ESS, endoscopic sinus surgery; DM, diabetes mellitus; SNOT-22, Sinonasal outcome test-22; RSDI, Rhinosinusitis disability index; BSIT, Brief Smell Identification Test. 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) 3×2 contingency tables.

Table 2.
Subjects using more antibiotics show less improvement in the SNOT-22 total score, mainly driven by the Rhinologic domain.

Mean improvement in clinical measures of disease severity and PROM scores stratified across preoperative antibiotic use (days out of previous 90 before ESS) groups (n=271)

PROMs:	1–14 Days Antibiotics (n=102)	15–28 Days Antibiotics (n=69)	29+ Days Antibiotics (n=100)	F-statistic	p-value
	Mean[SD]	Mean[SD]	Mean[SD]		
SNOT-22 total score	–28.6 [21.0] *	–28.2 [21.3] *	–21.5 [23.1] *	3.20	0.042
Rhinologic symptom domain	–8.9 [6.8] *	–8.3 [7.9] *	–5.6 [8.8] *	4.80	0.009
Extra-nasal rhinologic domain	–4.6 [3.5] *	–4.2 [4.0] *	–3.5 [4.3] *	1.92	0.149
Ear / facial symptom domain	–5.8 [5.2] *	–4.8 [5.2] *	–4.2 [5.2] *	2.59	0.077
Psychological dysfunction domain	–8.1 [8.6] *	–9.0 [8.3] *	–7.3 [8.7] *	0.85	0.428
Sleep dysfunction domain	–6.8 [6.9] *	–7.2 [6.5] *	–5.1 [6.8] *	2.41	0.092
RSDI total score	–24.2 [22.3] *	–27.4 [23.0] *	–21.7 [24.6] *	1.20	0.302
Physical domain	–10.1 [8.7] *	–11.0 [9.0] *	–8.5 [9.8] *	1.57	0.209
Functional domain	–8.3 [8.4] *	–9.3 [8.3] *	–7.4 [9.2] *	0.96	0.385
Emotional domain	–5.9 [7.8] *	–7.1 [7.9] *	–5.8 [8.5] *	0.66	0.515
Clinical Measure of Disease Severity					
Endoscopy scores	–3.5 [4.1] *	–3.2 [4.2] *	–2.7 [3.2] *	0.82	0.441
BSIT scores	0.3 [3.0]	–0.04 [2.8]	–0.04 [2.5]	0.40	0.671

PROM, patient-reported outcome measure; SD, standard deviation; SNOT-22, 22-item SinoNasal Outcome Test; RSDI, Rhinosinusitis Disability Index; BSIT, Brief Smell 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.

* indicates significant within-subjects improvement over time (p<0.001) using bivariate paired samples testing.

Table 3.
Subjects using more antibiotics were less likely to achieve an MCID in the SNOT-22 PROM.

Frequency of improvement by at least one MCID value in clinical measures of disease severity and PROM scores stratified across preoperative antibiotic use (days out of previous 90 before ESS) groups (n=271)

PROMs:	1–14 Days Antibiotics (n=102)	15–28 Days Antibiotics (n=69)	29+ Days Antibiotics (n=100)	χ^2	p-value
	N (%)	N (%)	N (%)		
SNOT-22 total score	87 (85%)	62 (90%)	73 (73%)	9.09	0.011
Rhinologic symptom domain	80 (78%)	47 (68%)	61 (61%)	7.29	0.026
Extra-nasal rhinologic domain	84 (82%)	51 (74%)	68 (68%)	5.58	0.061
Ear / facial symptom domain	78 (77%)	46 (67%)	61 (61%)	5.69	0.058
Psychological dysfunction domain	60 (59%)	45 (65%)	55 (55%)	1.77	0.414
Sleep dysfunction domain	63 (62%)	49 (71%)	60 (60%)	2.34	0.310
RSDI total score	72 (71%)	50 (73%)	60 (60%)	3.99	0.136
Physical domain	70 (69%)	51 (74%)	66 (66%)	1.20	0.549
Functional domain	70 (69%)	49 (71%)	58 (58%)	4.07	0.131
Emotional domain	57 (56%)	39 (57%)	55 (55%)	0.06	0.973
Clinical Measure of Disease Severity					
Endoscopy scores	50 (69%)	28 (62%)	35 (59%)	1.55	0.461
BSIT scores	20 (27%)	6 (12%)	19 (24%)	3.88	0.144

PROM, patient-reported outcome measure; SD, standard deviation; SNOT-22, 22-item SinoNasal Outcome Test; RSDI, Rhinosinusitis Disability Index; BSIT, Brief Smell Identification Test. P-values represent significant difference between at least 2 antibiotic use categories using omnibus chi-square (χ^2) testing and 4×2 contingency tables (“Improved vs Not Improved”) for independent groupings. MCID, minimal clinically important difference.

Table 4.
Antibiotic use demonstrated a weak negative correlation with improvement in the SNOT-22 Rhinologic domain after ESS.

Unadjusted linear regression effect estimates for the association between continuous preoperative antibiotic use days and mean postoperative changes in patient-reported outcome measures and clinical measures of disease severity in patients with CRS (n=271).

PROMs:	Unadjusted Effect Estimates of Preoperative Antibiotic Use Days					
	β	SE	95% CI [LB, UB]	t-test statistic	p-value	R
SNOT-22 total score	0.09	0.06	[-0.03, 0.21]	1.53	0.127	0.093
Rhinologic symptom domain	0.05	0.02	[0.01, 0.09]	2.37	0.019	0.143
Extra-nasal rhinologic domain	0.01	0.01	[-0.01, 0.03]	1.11	0.268	0.067
Ear / facial symptom domain	0.02	0.01	[-0.01, 0.05]	1.29	0.198	0.078
Psychological dysfunction domain	0.01	0.02	[-0.04, 0.05]	0.08	0.937	0.005
Sleep dysfunction domain	0.02	0.02	[-0.02, 0.06]	1.04	0.298	0.063
RSDI total score	0.03	0.06	[-0.10, 0.15]	0.45	0.653	0.027
Physical domain	0.03	0.03	[-0.02, 0.08]	1.06	0.292	0.064
Functional domain	0.01	0.02	[-0.04, 0.05]	0.36	0.717	0.022
Emotional domain	-0.01	0.02	[-0.05, 0.04]	-0.29	0.770	-0.018
Clinical Measure of Disease Severity						
Endoscopy scores	0.02	0.01	[-0.01, 0.04]	1.20	0.233	0.090
BSIT scores	-0.01	0.01	[-0.03, 0.01]	-0.80	0.427	-0.056

PROM, patient-reported outcome measure; SD, standard deviation; SNOT-22, 22-item SinoNasal Outcome Test; RSDI, Rhinosinusitis Disability Index; BSIT, Brief Smell Identification Test. SE, standard error of effect estimate. CI, confidence interval. LB, lower bound. UB, upper bound. ESS, endoscopic sinus surgery.

Table 5.
High antibiotic use was associated with lower likelihood of achieving an MCID in several SNOT-22 subdomains after ESS in unadjusted, but not multivariate, regression modeling.

Adjusted multivariate logistic regression effect estimates for the association between categorical preoperative antibiotic use days and prevalence of MCID changes in PROMs with statistically significant associations (n=271).

PROMs:	Effect Estimates of Preoperative Antibiotic Use Day Categories				
	β	SE	OR	OR 95% CI [LB, UB]	p-value
Unadjusted SNOT-22 total score:					
1–14 Days [Referent]	----	----	----	----	----
15–28 Days	0.42	0.49	1.53	[0.59, 3.97]	0.385
29+ Days	–0.76	0.36	0.47	[0.23, 0.94]	0.034
*Adjusted SNOT-22 total score:					
1–14 Days [Referent]	----	----	----	----	----
15–28 Days	0.67	0.51	1.94	[0.72, 5.28]	0.192
29+ Days	–0.33	0.39	0.72	[0.34, 1.53]	0.391

PROMs:	Effect Estimates of Preoperative Antibiotic Use Day Categories				
	β	SE	OR	OR 95% CI [LB, UB]	p-value
Unadjusted SNOT-22 rhinologic symptom score:					
1–14 Days [Referent]	----	----	----	----	----
15–28 Days	–0.53	0.35	0.59	[0.29, 1.17]	0.132
29+ Days	–0.84	0.32	0.43	[0.23, 0.80]	0.008
*Adjusted SNOT-22 rhinologic symptom score:					
1–14 Days [Referent]	----	----	----	----	----
15–28 Days	–0.40	0.34	0.61	[0.32, 1.39]	0.280
29+ Days	–0.49	0.17	1.05	[0.31, 1.19]	0.148

PROMs:	Effect Estimates of Preoperative Antibiotic Use Day Categories				
	β	SE	OR	OR 95% CI [LB, UB]	p-value
Unadjusted SNOT-22 extra-nasal rhinologic score:					
1–14 Days [Referent]	----	----	----	----	----
15–28 Days	–0.50	0.38	0.61	[0.29, 1.27]	0.186
29+ Days	–0.79	0.34	0.46	[0.24, 0.88]	0.019
*Adjusted SNOT-22 extra-nasal rhinologic score:					
1–14 Days [Referent]	----	----	----	----	----
15–28 Days	–0.33	0.40	0.72	[0.33, 1.56]	0.405
29+ Days	–0.59	0.35	0.55	[0.28, 1.11]	0.094

PROMs:	Effect Estimates of Preoperative Antibiotic Use Day Categories				
	β	SE	OR	OR 95% CI [LB, UB]	p-value
Unadjusted SNOT-22 ear / facial symptom score:					
1–14 Days [Referent]	----	----	----	----	----
15–28 Days	–0.49	0.35	0.62	[0.31, 1.21]	0.161
29+ Days	–0.73	0.31	0.48	[0.26, 0.89]	0.019
*Adjusted SNOT-22 ear / facial symptom score:					
1–14 Days [Referent]	----	----	----	----	----
15–28 Days	–0.38	0.36	0.68	[0.34, 1.38]	0.289
29+ Days	–0.57	0.32	0.57	[0.30, 1.06]	0.077

* Adjusted for enrollment site variation (p=0.976) and all covariates significant at the ~0.050 α -level including: age (p=0.010), nasal polyposis (p=0.058), revision surgery (p=0.006).

* Adjusted for enrollment site variation (p=0.780) and all covariates significant at the 0.050 α -level including: age (p=0.050), preoperative endoscopy score (p<0.001), revision surgery (p=0.005).

* Adjusted for enrollment site variation (p=0.686) and all covariates significant at the 0.050 α -level including: preoperative endoscopy score (p<0.001) and revision surgery (p=0.001).

* Adjusted for enrollment site variation (p=0.868) and all covariates significant at the 0.050 α -level including: preoperative CT score (p=0.031), revision surgery (p=0.032), and inferior turbinate reduction procedures (p=0.041).