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General Antibiotic Exposure Is Associated with Increased Risk of Developing Chronic Rhinosinusitis

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Objective: Antibiotic use and chronic rhinosinusitis (CRS) have been independently associated with microbiome diversity depletion and opportunistic infections. This study was undertaken to investigate whether antibiotic use may be an unrecognized risk factor for developing CRS.

Study Design: Case-control study of 1,162 patients referred to a tertiary sinus center for a range of sinonasal disorders.

Methods: Patients diagnosed with CRS according to established consensus criteria (n = 410) were assigned to the case group (273 without nasal polyps [CRSsNP], 137 with nasal polyps [CRSwNP]). Patients with all other diagnoses (n = 752) were assigned to the control group. Chronic rhinosinusitis disease severity was determined using a validated quality of life (QOL) instrument. The class, diagnosis, and timing of previous nonsinusitis-related antibiotic exposures were recorded. Results were validated using a randomized administrative data review of 452 (38.9%) of patient charts. The odds ratio of developing CRS following antibiotic exposure were calculated, as well as the impact of antibiotic use on the subsequent QOL.

Results: Antibiotic use significantly increased the odds of developing CRSsNP (odds ratio: 2.21, 95% confidence interval, 1.66–2.93, $P < 0.0001$) as compared to nonusers. Antibiotic exposure was significantly associated with worse CRS QOL scores ($P = 0.0009$) over at least the subsequent 2 years. These findings were confirmed by the administrative data review.

Conclusion: Use of antibiotics more than doubles the odds of developing CRSsNP and is associated with a worse QOL for at least 2 years following exposure. These findings expose an unrecognized and concerning consequence of general antibiotic use.

Key Words: Antibiotics, side effects, microbiome, chronic rhinosinusitis, quality of life.

Level of Evidence: 3b.

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INTRODUCTION

The discovery of antibiotics is considered one of the major technological advances in medicine, enabling a variety of modern procedures and the treatment of previously mortal infections.[1] These substantial benefits however, have come with significant costs. Widespread overuse has led to the evolution of resistant organisms among virtually all classes of antibiotics.[2] Ambulatory care visits in the United States result in an estimated annual rate of 506 antibiotic prescriptions per 1,000 U.S. population.[3] Across all conditions, an estimated 30% of outpatient oral antibiotic prescriptions are inappropriate.[3] Overuse of antibiotics has also resulted in expanding healthcare costs, leading to a variety of new practice guidelines.[4,5] The United Kingdom has already realized an estimated savings of £3,678,000 per year following the recent adoption of the National Institute of Clinical Excellence guideline CG69 advising against the prescription of antibiotics for self-limiting respiratory tract infections.[2] Antibiotics have also been associated with significant adverse side effects. It has long been recognized that antibiotic use may lead to increased susceptibility to secondary mucosal infections from pathogens including *Candida albicans* and *Clostridium difficile*.[6–8] Recent studies on the concept of mucosal microbial dysbiosis have suggested that these infections arise as a result of antibiotic-induced depletion of the diverse commensal microbial assemblage, which enables the proliferation of pathogenic species.[9]

Chronic rhinosinusitis (CRS) impacts more than 30 million Americans, resulting in $6.9 to $9.9 billion in annual healthcare expenditures.[10,11] The diagnosis of both acute and CRS is the most common cause for antibiotic prescriptions of all primary diagnoses in ambulatory care visits.[12] Chronic rhinosinusitis is defined by both the American Academy of Otolaryngology–Head and Neck Surgery Foundation[13] and the European Position Paper on Rhinosinusitis and Nasal Polyps[14] as

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TABLE I.
Characteristics of the Case Patients and Controls

Variable	Case Patients (N = 410)		Control Patients (N = 752)	
	Antibiotic Naïve (N = 179)	Antibiotic Exposed (N = 231)	Antibiotic Naïve (N = 436)	Antibiotic Exposed (N = 316)
Age-yr*	49 (19–87)	50 (17–88)	46 (15–89)	46 (13–92)
Gender				
Male-no. (%)	102 (56.98)	113 (48.92)	214 (49.08)	106 (33.54)
Female-no. (%)	77 (43.02)	118 (51.08)	222 (50.92)	210 (66.46)
Comorbidity				
Asthma-no. (%)	45 (25.14)	79 (34.20)	77 (17.66)	86 (27.22)
Environmental Allergy-no. (%)	98 (54.75)	150 (64.94)	231 (52.98)	179 (56.65)
Aspirin Exacerbated Respiratory Disease-no. (%)	4 (2.23)	12 (5.19)	1 (0.23)	1 (0.32)
Smoker-no. (%)	10 (5.59)	15 (6.49)	41 (9.40)	26 (8.23)
No. Pack per Day*	0.0 (0.0–1.5)	0.0 (0.0–1.5)	0.0 (0.0–1.0)	0.0 (0.0–3.0)
Presenting Diagnosis-no. (% all patients)**				
CRSsNP	105 (7.02)	168 (11.23)	0 (0.00)	0 (0.00)
CRSwNP	74 (4.95)	63 (4.21)	0 (0.00)	0 (0.00)
Nasal Obstruction	44 (2.94)	56 (3.74)	204 (13.64)	135 (9.02)
Allergic Rhinitis	12 (0.80)	7 (0.47)	118 (7.89)	72 (4.81)
Mucocele	3 (0.20)	2 (0.13)	4 (0.27)	5 (0.33)
Rhinitis Medicomentosa	2 (0.13)	0 (0.00)	7 (0.47)	3 (0.20)
Nonsinogenic Smell Disorder	2 (0.13)	3 (0.20)	6 (0.40)	3 (0.20)
Sinonasal Tumor	2 (0.13)	0 (0.00)	27 (1.80)	13 (0.87)
Nonsinogenic Headache	2 (0.13)	11 (0.74)	78 (5.21)	77 (5.15)
Cough	1 (0.07)	0 (0.00)	3 (0.20)	3 (0.20)
Gastroesophageal Reflux	1 (0.07)	3 (0.20)	17 (1.14)	21 (1.40)
Graves' Orbitopathy	0 (0.00)	0 (0.00)	3 (0.20)	1 (0.07)
Cerebrospinal Fluid Leak/Encephalocele	0 (0.00)	0 (0.00)	4 (0.27)	3 (0.20)
Maxillary Sinus Atelectasis	0 (0.00)	0 (0.00)	2 (0.13)	5 (0.33)
Maxillary Sinus Retention Cyst	0 (0.00)	1 (0.07)	3 (0.20)	7 (0.47)
Nasolacrimal Duct Obstruction	0 (0.00)	0 (0.00)	9 (0.60)	12 (0.80)
Vasomotor Rhinitis	0 (0.00)	0 (0.00)	20 (1.34)	6 (0.40)
Epistaxis	0 (0.00)	0 (0.00)	36 (2.41)	27 (1.80)

*Median (Min - Max), **Includes patients with multiple diagnoses
CRSsNP=Chronic Rhinosinusitis without Nasal Polyps, CRSwNP=Chronic Rhinosinusitis with Nasal Polyps

having greater than 12 weeks of sinonasal symptoms, along with at least one objective measure of infection or inflammation by nasal endoscopy or radiographic imaging. Studies on the pathogenesis of CRS have proposed multiple etiologic agents, including bacteria,[15] fungus,[16] and biofilms,[17] resulting in chronic infection with associated mucosal inflammation. However the distinct lack of long-term disease resolution following antimicrobial therapy,[18,19] and in some cases surgery,[20] suggests that additional factors are likely involved. Through these studies, CRS with nasal polyps (CRSwNP) has been recognized as an inflammatory subtype characterized by eosinophilic inflammation and a T-helper cell type 2 immunologic profile.[21–23] Although CRSwNP lacks the features of a classic infectious process, the precise role of bacteria and their byproducts in the promotion of nasal polyp-related inflammation remains unclear.[24]

Recent findings from culture independent investigations of the sinonasal microbiome have offered new insights into the pathogenesis of CRS. These studies have suggested that a decreased microbial diversity exists in CRS patients as compared to healthy controls with a selective enrichment of pathogenic species.[25–27] Furthermore, some studies have shown that antibiotic exposure may be a risk factor associated with this loss of biodiversity,[25] echoing the findings seen in postantibiotic *C. difficile* infections.[9] Although systemic antibiotics have long been a mainstay of therapy for CRS,[20] these findings lead inexorably to the paradoxical hypothesis that antibiotic exposure may, in fact, promote its onset. The purpose of this study was therefore to investigate whether premorbid antibiotic exposure is an unrecognized risk factor for the diagnosis of CRS, whether it confers a risk of greater disease severity, and to determine the time horizon for such an effect.

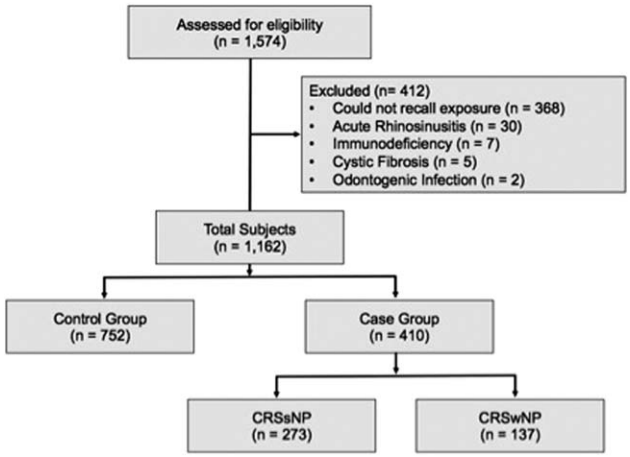

Fig. 1. Flow diagram of patient inclusion and exclusion criteria. CRSsNP = chronic rhinosinusitis without nasal polyps; CRSwNP = chronic rhinosinusitis with nasal polyps.

MATERIALS AND METHODS

We performed a Massachusetts Eye and Ear Infirmary Institutional Review Board-approved (approval number 14-186H) case control study of 1,574 patients referred to the Massachusetts Eye and Ear Infirmary Sinus Center in 2014 with symptoms of presumed sinonasal disease. This study was designed according to Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.[28] Patients were evaluated for the presence of CRS by one of four rhinology subspecialists according to strict consensus diagnostic criteria,[13,14] which included a directed history, sinonasal endoscopy, and computed tomography imaging. A validated disease-specific quality-of-life (QOL) survey (22-item Sinonasal Outcome Test [SNOT]),[29] demographic data, and antibiotic history were obtained for all patients. This history included the class, diagnosis, and timing of any prior antibiotic exposures for at least the preceding 2 years. The diagnosing rhinologist was blinded to the responses of the patient who, in turn, was blinded to the purpose of the survey. Inclusion criteria included all antibotic-naïve patients, and all antibiotic exposed patients for whom antibiotic use was for nonsinonasal-related infections. Among the antibiotic exposed group, only patients who used antibiotics for nonsinonasal-related infections prior to the onset of symptoms of CRS (within the case group) were enrolled in the study. Additional exclusion criteria included patients who could not recall any specific details regarding their exposures (n = 368), those with new onset acute rhinosinusitis (n = 30), and those with confounding diseases independently associated with both CRS and an increased risk of antibiotic use. These included immunodeficiency (n = 7), cystic fibrosis (n = 5), and maxillary dental infections (n = 2). Of the remaining 1,162 patients, those with confirmed CRS were assigned to the case group (n = 410), whereas all other diagnoses were assigned to the control group (n = 752) (see Table I). The case group was further substratified into CRS patients without nasal polyps (CRSsNP, n = 273) and with nasal polyps (CRSwNP, n = 137) based on the presence of nasal polyps on sinonasal endoscopy (see Fig. 1).

In order to validate the accuracy of self-reported antibiotic exposure, we performed a randomized chart review of 452 patients, including at least 10% of patients within each reported exposure time, which is the accepted level in similar studies in the literature.[30] These patients had their comprehensive care within our medical record system. Standard descriptive statistics were reported, median (minimum–maximum) for numerical variables and frequency count (%) for categorical variables. Chi-square tests were performed to examine the association between categorical patient characteristics and CRS. Odds ratios with 95% confidence intervals were also calculated for all patients with CRS, as well as the CRSsNP and CRSwNP subgroups. Wilcoxon rank-sum tests or Kruskal-Wallis tests were used for the comparison of numerical variables, including SNOT-22 scores between cases (all CRS and CRS subgroups) and controls, among patients using different antibiotic classes, among patients with different underlying reasons for antibiotics, and among patients with different times since last antibiotic use. Individual data points among these comparisons that could not be recalled were excluded from the relevant subanalysis. In addition, logistic regression was performed to examine the effect of antibiotic exposure on CRS after adjusting for other covariates, including gender, asthma, environmental allergy, aspirin-exacerbated respiratory disease, smoking, and age. The population attributable risk within our study population was calculated according to previously described methods.[31] All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC). There was no funding source for this study.

RESULTS

Among the case patients, 56.34% reported a previous nonsinus-related antibiotic exposure as compared to 42.02% of control patients. Antibiotic use significantly increased the odds of developing both CRSsNP (odds ratio [OR]: 2.21, 95% confidence interval [CI], 1.66–2.93, $P < 0.0001$) and any form of CRS (OR: 1.78, 95% CI 1.40–2.27, $P < 0.0001$) as compared to nonusers. This odds ratio was similar even when excluding patients who were treated for upper aerodigestive infections. In contrast, antibiotic exposure did not significantly impact the odds of developing CRSwNP (OR: 1.17, 95% CI 0.81–1.69, $P = 0.39$). The percent of patients with any form of CRS and CRSsNP only, which was attributable to a previous exposure to antibiotics, was 24.69% (95% CI 14.38–34.79) and 33.70% (95% CI 21.70–44.77), respectively. In both the case and control groups, the most common class of antibiotic patients received was a penicillin (52.63% vs. 45.77%), and the most common reported reason for antibiotic prescription was the diagnosis of pharyngitis(18.06% vs. 16.67%) (see Table II).

As expected,[32] the presence of asthma, aspirin-exacerbated respiratory disease, and environmental allergy were significantly higher in the case group ($P < 0.01$, $P < 0.001$, and $P = 0.02$; respectively) relative to the control group. The case group also had a significantly higher median age (49.5 yrs, 17–88 yrs; median, minimum–maximum) and preponderance of male patients (52.44%) as compared to the control group (46.0 years, 13–92 years, $P = 0.01$ and 42.55%, $P < 0.01$, respectively). However there were no significant differences with respect to smoking status ($P = 0.09$) or the number of packs smoked per day ($P = 0.14$). Additionally, among antibiotic users, no significant differences were found between groups with respect to the spectrum of antibiotic classes used ($P = 0.50$) or the underlying reason for antibiotic use ($P = 0.85$). Finally, the logistic regression confirmed that antibiotic use still had a significant impact on the development of CRS (adjusted OR: 1.80,

TABLE II.
Odds Ratios for Chronic Rhinosinusitis Associated with Antibiotic Use

Variable-no. (%)		Case Patients (N = 410)	Control Patients (N = 752)	Odds Ratio (95%CI)*
All CRS				
Antibiotic Exposure				
	Naïve	179 (43.65)	436 (57.98)	1.00 (Reference)
	Exposed	231 (56.34)	316 (42.02)	1.78 (1.40–2.27)
Antibiotic Class				
	Penicillin	50 (52.63)	65 (45.77)	1.00 (Reference)
	Macrolide	14 (14.74)	36 (25.35)	0.51 (0.25–1.04)
	Tetracycline	10 (10.53)	11 (7.75)	1.18 (0.47–3.00)
	Fluoroquinolone	8 (8.42)	15 (10.56)	0.69 (0.27–1.76)
	Sulfonamide	5 (5.26)	5 (3.52)	1.30 (0.36–4.74)
	Cephalosporin	3 (3.16)	4 (2.82)	0.98 (0.21–4.56)
	Glycopeptide	2 (2.11)	1 (0.70)	2.60 (0.23–29.49)
	Lincosamide	2 (2.11)	2 (1.41)	1.30 (0.18–9.55)
	Rifamycin	1 (1.05)	0 (0.00)	–
	Nitrofuran	0 (0.00)	2 (1.41)	–
	Nitroimidazole	0 (0.00)	1 (0.70)	–
Type of Infection				
	Pharyngitis	26 (18.06)	38 (16.67)	1.00 (Reference)
	Cellulitis	17 (11.81)	27 (11.84)	0.92 (0.42–2.02)
	Genitourinary	17 (11.81)	30 (13.16)	0.83 (0.38–1.80)
	Pneumonia	17 (11.81)	23 (10.09)	1.08 (0.48–2.41)
	Surgical Prophylaxis	17 (11.81)	29 (12.72)	0.86 (0.39–1.87)
	Bronchitis	15 (10.42)	29 (12.72)	0.76 (0.34–1.68)
	Otitis	15 (10.42)	32 (14.04)	0.69 (0.31–1.51)
	Gastrointestinal	10 (6.94)	10 (4.39)	1.46 (0.53–4.01)
	Central Nervous System	7 (4.86)	5 (2.19)	2.05 (0.59–7.15)
	Ocular	3 (2.08)	5 (2.19)	0.88 (0.19–3.99)
CRSsNP				
Antibiotic Exposure				
	Naïve	105 (38.46)	436 (57.98)	1.00 (Reference)
	Exposed	168 (61.54)	316 (42.02)	2.21 (1.66–2.93)
CRSwNP				
Antibiotic Exposure				
	Naïve	74 (54.01)	436 (57.98)	1.00 (Reference)
	Exposed	63 (45.99)	316 (42.02)	1.17 (0.81–1.69)

*CI-Confidence Interval, CRS-Chronic Rhinosinusitis
CRSsNP=Chronic Rhinosinusitis without Nasal Polyps, CRSwNP=Chronic Rhinosinusitis with Nasal Polyps

95% CI, 1.40–2.31, $P < 0.0001$) even after adjusting for the other potential confounders.

Among the CRS patients (i.e., case group), the use of antibiotics was significantly associated with worse QOL scores (42.0, 4–104; median, minimum–maximum) as compared to antibiotic-naïve CRS patients (33.5, 3–107; $P = 0.0009$). The effect on QOL was enduring because patients who used antibiotics at least 2 years prior to the development of CRS (36.81%) had similar disease severity scores as compared to those with more recent exposures. There was no significant difference in QOL score among patients using different antibiotic classes and among patients with different underlying reasons for antibiotic use ($P = 0.20$ and 0.26, respectively) (see Table III).

The review of administrative data revealed an overall rate discordance between reported and actual antibiotic use of 11.95%. The reported antibiotic exposed case and control groups had lower discordant rates (5.89% and 4.12%, respectively) as compared to those who reported being antibiotic-naïve (12.94% and 13.91%, respectively). Within the administrative data set, antibiotic exposure significantly increased the odds of developing any form of CRS (OR: 4.90, 95% CI, 2.10–11.37, $P = 0.0002$) as compared to those who were antibiotic-naïve, which is consistent with the patient-reported data.

TABLE III.
Variables Associated With CRS Quality of Life (QOL)

Variable			QOL Score Median	(Minimum–Maximum)	*P* Value
All CRS					
	Antibiotic exposure				
		Naïve	33.5	(3–107)	< 0.01*
		Exposed	42.0	(4–104)	
	Antibiotic class				
		Penicillin	40.0	(4–104)	0.20†
		Macrolide	35.5	(8–92)	
		Tetracycline	46.0	(29–85)	
		Fluoroquinolone	41.0	(16–67)	
		Sulfonamide	41.0	(15–78)	
		Cephalosporin	33.0	(18–35)	
		Glycopeptide	42.5	(12–73)	
		Lincosamide	8.5	(7–10)	
		Rifamycin	9.0	(9–9)	
	Type of infection				
		Pharyngitis	43.0	(10–92)	0.26†
		Cellulitis	44.0	(5–100)	
		Genitourinary	41.0	(23–79)	
		Pneumonia	47.0	(15–89)	
		Surgical prophylaxis	32.0	(6–69)	
		Bronchitis	45.5	(4–104)	
		Otitis	47.0	(15–76)	
		Gastrointestinal	27.5	(9–72)	
		Central nervous system	46.0	(16–85)	
		Ocular	26.0	(19–48)	
	Time since last use				
		> 2 years	42.0	(9–104)	0.45†
		1–2 years	50.0	(14–89)	
		6 months–1 year	43.0	(9–100)	
		3–6 months	39.5	(5–84)	
		1–3 months	49.0	(7–92)	
CRSsNP					
	Antibiotic exposure				
		Naïve	34.0	(3–94)	0.02*
		Exposed	42.0	(4–104)	
CRSwNP					
	Antibiotic exposure				
		Naïve	32.0	(6–107)	0.01*
		Exposed	48.0	(9–100)	

*Wilcoxon rank-sum Test.
†Kruskal-Wallis Test.
CRS = chronic rhinosinusitis; CRSsNP = chronic rhinosinusitis without nasal polyps; CRSwNP = chronic rhinosinusitis with nasal polyps.

DISCUSSION

The human microbiome project has provided new insights into the distribution and abundance of bacterial species in both health and disease.[33] Opportunistic *pathogens*, as defined by the pathosystems resource integration center, were found nearly ubiquitously in the nares of healthy subjects, albiet at relatively low abundance.[34] Additional studies of the normal nasal cavity found an inverse correlation between the prevalence of Firmicutes such as *S. aureus* and benign commensal organisms, suggesting a homestatic anatagonism between potential pathogens and the remainder of the *healthy* microbial assemblage.[35] Extrapolation of this concept would therefore predict that events resulting in a perturbation or loss of the commensal microbial community would enable proliferation of pathogenic species,

resulting in the disease phenotype. This prediction has borne out in several studies of the sinonasal microbiome in patients with CRS. Feazel et al. found a decreased number of bacterial types and an overabundance of *S. aureus* among CRS patients as compared to controls.[25] Antibiotic exposure was one of the most significant clinical factors driving this effect.[25] Similar findings were published by Choi et al.[26] and Abreu et al.[27] Liu et al.[20] directly addressed the impact of antibiotic exposure on the microbiome of patients with CRS, demonstrating a consistent loss of diversity and eveness within the same patient immediately following treatment. Although literature regarding the sinonasal microbiome in health and disease remains nascent, it has provided some limited clues that antibiotics may lead to a reduction of sinonasal microbial biodiversity, which in turn may be a significant feature of CRS.

In light of the broad potential clinical implications of such a finding, we employed a case-control design using only patients evaluated for CRS by a group of subspecialists according to strict consensus criteria.[13,14] Although our results are subject to the intrinsic limitations of a case-control study, this technique represents the only practical method to examine this phenomenon. A prospective randomized placebo controlled study would neither be feasible based on the required power, nor ethical because it would mandate denying antibiotics to patients with established infections. Similarly, the use of large population-based registries and databases would yield inaccurate results because it would both underrepresent patients with CRS who had not yet been diagnosed and include patients misdiagnosed with CRS, a frequent occurrence in patients with certain forms of headache.[36] This is reflected in our own study population, where nonsinogenic headache represented the fourth most common diagnosis among patients referred for presumed sinus disease. One concern regarding our study design was the potential for inclusion of patients with confounding diagnoses that would predispose to both antibiotic use and CRS. This was mitigated through the a priori exclusion of known confounding populations[20] and a post hoc logistic regression analysis, which confirmed the influence of antibiotic use on the development of CRS even after adjusting for the residual confounders. A second concern was the possibility of recollection bias, which could overestimate the calculated odds ratio if patients with CRS were more likely to recall previous antibiotic exposures than control patients. In order to mitigate this possibility, we validated our findings using an administrative data review. These results demonstrated a high concordance between patient-reported exposures and actual prescription data over all of the time points, and independently confirmed an increased risk of CRS in patients with a history of antibiotic exposure. The concordance rate was found to be 88% based on our data review, which is an acceptable level in similar studies in the literature.[30,37] Furthermore, our analysis found that that the queried historical variables were comparable across the case and control patients. This confirms that any potential recollection biases were relatively evenly balanced among the two groups.

Our results demonstrate that exposure to antibiotics is a significant risk factor for the development of CRS and accounts for approximately 25% of the disease burden in our study population. These findings harmonize with the predictions of the nascent literature on the sinonasal microbiome.[18,26] This effect was primarily driven by the CRSsNP subgroup, which also supports the evolving concept of CRSwNP as a disease of primary inflammation rather than infection.[38,39] Despite this, we elected to analyze the CRS group as a whole because the precise relationship between CRS with and without nasal polyps remains incompletely understood, and it is possible that a proportion of the CRSsNP patients could go on to develop nasal polyps over time.[38] The wide range of ages and disease types found within our population, coupled with the prevalence of general antibiotic prescription,[12] suggests that these results may be reasonably applicable to the overall population. The fact that antibiotic exposure was additionally associated with a worse quality of life comports with prior studies,[20,25] which strongly favor the depletion of microbial diversity as a candidate mechanism for this relationship. However, it is important to stress that this study is not designed to interrogate causality, and the associations reported may be confounded by some proportion of case patients who had already begun to experience subclinical CRS prior to their reported antibiotic exposure.

One unexpected outcome of our study was that a large percentage of exposures preceeded the onset of the diagnosis of sinusitis by more than 2 years. This indicates that, regardless of the mechanism, the sequelae of antibiotic use may endure much longer then previously thought.[40] The fact that we could not isolate this effect to any single agent or underlying premorbid infection suggests that this risk must be taken into consideration when prescribing any class of antibiotic, regardless of the type of infection.

The impact of antibiotics on promoting bacterial resistance,[41] and the development of mucosal infections from pathogens such as *C. difficile* and *C. albicans*, has been well established.[6–9] This study demonstrates that antibiotics also significantly increase the risk of developing CRS, an effect that is driven primarily by CRS patients who do not have nasal polyps. Furthermore, premorbid antibiotic use could account for approximately 25% of our patients who developed CRS, and exposure conferred a worse disease-specific quality of life. These findings have important implications, not only for practitioners who treat patients with sinus disease, but across the breadth of medical specialties where the prescription of antibiotics for all causes must be continue to be carefully weighed against the potential risks.

CONCLUSION

The use of antibiotics for nonsinonasal-related infections more than doubles the risk of developing CRSsNP and is associated with worse quality of life. A putative reduction in microbial diversity may play a role

in this finding; however, further studies are needed to elucidate this relationship. In practice, the prescription of antibiotics must be carefully considered against possible long-term sequelae.

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Author Contributions: B.S.B. developed the concept, designed the study protocol, and drafted the article. A.M., B.S.B., N.Y.B., S.T.G., and E.H.H., H.K., and L.G. assisted in the acquisition of the data. R.G. performed the biostatistical analysis. All authors participated in critical revision, approved the final article, and agree to be accountable for all aspects of the work.

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