Prophylactic antibiotics after endoscopic sinus surgery for chronic rhinosinusitis: a randomized, double-blind, placebo-controlled noninferiority clinical trial

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Background: Surgeons commonly prescribe prophylactic antibiotics after endoscopic sinus surgery (ESS), yet minimal data exist to support this practice. In this study we aimed to assess the impact of post-ESS antibiotics on infection, quality of life (QOL), and endoscopic scores.

Methods: This was a randomized, double-blind, placebo-controlled, noninferiority trial comparing amoxicillin-clavulanate vs placebo after ESS (NCT01919411, ClinicalTrials.gov). Adults (N = 77) with chronic rhinosinusitis (CRS) refractory to appropriate medical therapy who underwent ESS were randomized to antibiotics (N = 37) or placebo (N = 40) and followed clinically (mean ± standard deviation: 1.3 ± 0.3 and 8.8 ± 3.9 weeks postoperatively). At baseline and follow-up, QOL was measured with 22-item Sino-Nasal Outcome Test questionnaires and Lund-Kennedy endoscopic scores were evaluated. Outcomes were analyzed with repeated-measures analysis of variance and analysis of covariance and *z* tests for proportions.

Results: Placebo was noninferior to antibiotic prophylaxis with regard to postoperative SNOT-22 scores ($\beta = 0.18$, 2-tailed $p < 0.05$). There were no significant differences between the antibiotic and placebo groups in LK score trajectories over time ($p = 0.63$) or in postoperative infection rates (2.6% vs 2.4%, respectively; $p = 0.96$). The rate of diarrhea was significantly higher in the antibiotic group (24.3% vs 2.5%; relative risk = 10.8; $p = 0.02$).

Conclusion: Although statistically underpowered, the results suggest placebo was noninferior to prophylactic antibiotics after ESS for CRS regarding postoperative sinonasal-specific QOL. There were no significant differences in postoperative endoscopic scores or rates of infection, but the rate of diarrhea was significantly higher in the antibiotic group. These findings add to the growing evidence that routine use of prophylactic postoperative antibiotics does not improve outcomes post-ESS and significantly increases the rate of diarrhea.

Key Words:
chronic rhinosinusitis; endoscopic sinus surgery; evidence-based medicine; postoperative; quality of life; patient-reported outcome measure

How to Cite this Article:
Lehmann AE, Raquib AR, Siddiqi SH, et al. Prophylactic antibiotics after endoscopic sinus surgery for chronic rhinosinusitis: a randomized, double-blind, placebo-controlled noninferiority clinical trial. *Int Forum Allergy Rhinol.* 2020;00:1-9.

It is debated whether antibiotics are routinely needed immediately after endoscopic sinus surgery (ESS) for chronic rhinosinusitis (CRS) to mitigate the risk of postoperative infection, decrease mucosal inflammation, and optimize patient outcomes.[1–3] As >250,000 sinus surgeries are conducted annually in the United States,[4]

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Potential conflict of interest: None provided.

Presented as a virtual oral presentation at the annual meeting of the American Rhinologic Society at the American Academy of Otolaryngology–Head and Neck Surgery conference on September 10, 2020.

Received: 30 September 2020; Revised: 25 November 2020; Accepted: 29 November 2020
DOI: 10.1002/alr.22756
View this article online at wileyonlinelibrary.com.

practice patterns of post-ESS antibiotic usage may wield substantial impact on antibiotic resistance, health-care costs, quality of life (QOL), and the risk of potentially harmful antibiotic-related side effects.[5,6] Four previous randomized, controlled trials have investigated prophylactic antibiotic use after ESS; however, these studies merely reported that antibiotics offer either: (1) no significantly greater improvement in postoperative symptoms or endoscopic scores relative to placebo[7,8] and control[9]; or (2) only modest, transient greater improvement from antibiotics relative to placebo.[10] No previous trial has assessed whether withholding antibiotics is specifically *noninferior* to administering prophylactic antibiotics post-ESS with regard to outcomes for patients with CRS. Nor have any of these earlier trials utilized both a well-validated patient-reported outcome measure[7,9,10] and a standard duration of postoperative antibiotics.[8]

In this study, we sought to investigate the potential noninferiority of withholding prophylactic antibiotics after ESS utilizing a well-validated instrument for sinonasal-specific outcomes for patients with CRS, the 22-item Sino-Nasal Outcome Test (SNOT-22).[11] We conducted a randomized, double-blind, placebo-controlled noninferiority trial to compare prophylactic amoxicillin-clavulanate with placebo for 1 week post-ESS to assess the impact of postoperative antibiotics on outcomes after ESS, including sinonasal QOL, endoscopic scores, infection rates, and antibiotic-related side effects. We hypothesized that the sinonasal QOL of patients taking placebo would be noninferior to that of patients taking antibiotics post-ESS.

Patients and methods

Trial design

This study was a single-center, block-randomized, double-blind, placebo-controlled, parallel-group, noninferiority trial comparing prophylactic amoxicillin-clavulanate with placebo after ESS. Patients were recruited from a rhinology clinic at a tertiary care center in the United States. Participants were followed for 8.8 ± 3.9 (mean ± standard deviation [SD]) weeks after ESS. No interim analyses for efficacy or futility were conducted. The study was approved by the institutional review board of Massachusetts Eye and Ear and registered at ClinicalTrials.gov (NCT01919411).

Participants

Eligible patients were adults with CRS, as defined by the 2007 and 2015 consensus statements of the American Academy of Otolaryngology–Head and Neck Surgery.[5,12] These patients had been determined by their surgeon to have persistent symptoms despite appropriate medical therapy and were offered ESS. Study recruitment occurred in the Massachusetts Eye and Ear Sinus Center (Boston, MA), a high-volume tertiary care hospital clinic associated with the Department of Otolaryngology–Head and Neck Surgery of Harvard Medical School. Eligible patients were referred for enrollment, which was conducted by the research coordinator, and provided informed consent if they wished to participate. Participants' exclusion criteria were age <18 years, allergy to study drug or related medications (ie, penicillins or cephalosporins); systemic antibiotic treatment within 1 week preoperatively, cystic fibrosis, immunodeficiency, pregnancy, odontogenic sinusitis, complicated sinusitis (ie, any adverse progression of a sinus infection beyond the paranasal sinuses such that there was soft tissue, orbital, or intracranial involvement, including cellulitis, orbital abscess formation, or meningitis[5]), fungal ball, infected mucocele, nonendoscopic sinus surgery (eg, Caldwell-Luc or external approach), active sinus infection identified intraoperatively, intraoperative complication, or foreign body placement (eg, surgical stent or absorbable/nonabsorbable packing). An active sinus infection was defined as discolored purulent secretions with underlying mucosal inflammation seen on intraoperative sinonasal endoscopy. Thick secretions alone (without the appearance of pus and mucosal inflammation) were not considered to be indicative of a sinus infection intraoperatively, but assessments erred on the side of infection. Participants in the present trial were similar to patients included in previous trials assessing postoperative antibiotic usage after ESS.[7–10]

Intervention

Study participants underwent uncomplicated ESS (performed by S.T.G. or E.H.H.). One gram of cefazolin was given intravenously within 1 hour before surgery to all participants per standard surgical prophylaxis. Cultures were obtained from the sinuses after completion of the surgery. Participants were randomized to receive either antibiotic or placebo postoperatively in a double-blind manner. Amoxicillin-clavulanate (500-125 mg) was selected as the intervention as it is commonly used for postoperative prophylaxis after ESS. Other trials have utilized amoxicillin-clavulanate as well but with alternative doses (375 mg given 3 times daily[9] and 625 mg given twice daily[10]). The first dose of the study drug (antibiotic or placebo) was administered in the recovery room approximately 2 hours postoperatively once participants were awake, alert, and oriented. The morning after surgery, participants began self-administering the study drug twice daily for 1 week.

Objectives

The objective of the trial was to assess the impact of postoperative prophylactic antibiotics on outcomes after ESS, including sinonasal QOL, endoscopic scores, and infection rates. Before data collection, we hypothesized that the sinonasal QOL of patients taking placebo would be noninferior to that of patients taking prophylactic antibiotics post-ESS.

Outcomes

The primary outcome was change from baseline in sinonasal-specific QOL, as measured by the validated instrument SNOT-22. Higher SNOT-22 scores (range, 0-110) indicate more severe symptoms. SNOT-22 questionnaires were completed by participants at the preoperative visit (approximately 1 month pre-ESS) and at 2 postoperative visits (approximately 1 and 9 weeks post-ESS). Patients were instructed to reflect on their current symptoms since the surgery (not before surgery) when completing the SNOT-22 questionnaire to most reliably capture their postoperative sinonasal-specific QOL. No other randomized, controlled trial of nonmacrolide antibiotics post-ESS has utilized SNOT-22 scores to evaluate outcomes.[13]

Secondary outcomes were change from baseline of the Lund-Kennedy (LK) sinonasal endoscopic score[14] and rate of postoperative infection. The LK grading system allows for visual evaluation of the sinonasal cavities along 5 domains: polyps, edema, discharge, scarring, and crusting.[14] Higher LK scores (range, 0-20) indicate greater sinus disease.[14] The surgeons (blinded) performed endoscopy to assign LK scores and to evaluate for the presence of a sinus infection at the time of surgery and at the 2 postoperative visits. A postoperative sinus infection was defined as discolored purulent secretions with underlying mucosal inflammation visualized during postoperative sinonasal endoscopy. Thick secretions alone (without the appearance of pus and mucosal inflammation) were not considered to be indicative of a sinus infection postoperatively. Additional exploratory analyses included baseline demographics, clinical characteristics, sinonasal culture growth, and rates of diarrhea.

Sample size

Sample size was calculated based on a 2-group noninferiority design. The SNOT-22 between-patient SD of the within-patient change from baseline to follow-up was estimated to be 20 based on earlier reports of patients undergoing ESS for CRS.[11] The noninferiority threshold was estimated as 9, which is considered the smallest difference detectable by patients, known as the minimal clinically important difference (MCID).[11] Based on this a priori noninferiority margin, a minimum sample size of 214 participants (107 per group) was needed to achieve 95% power (2-tailed $p < 0.05$). Due to concern for confounding from unobserved time trends, the study was stopped upon approaching 5 years of study recruitment.

Randomization and blinding

Participants were randomly assigned to 1 of 2 parallel groups, in a 1:1 allocation ratio, to receive antibiotic or placebo. Randomization was conducted in blocks of 2 to increase the likelihood of an even allocation between groups. After providing consent, each participant's name, medical record number, allergies, enrollment date, and study identification number were sent to the clinical pharmacist, who determined the intervention (antibiotic vs placebo) on the day of surgery according to a computer-generated randomization list and dispensed the assigned study medication to the participant in the recovery room. The antibiotic and placebo were identical in appearance and prepacked in bottles, consecutively numbered for each participant according to the randomization schedule. The allocation sequence was concealed from participants and from study staff until the study was completed. Randomization documentation was stored securely in a locked file cabinet inside a locked office of the pharmacy.

Statistical methods

A noninferiority test was used to assess whether placebo was noninferior to prophylactic antibiotics after ESS with regard to SNOT-22 score change from baseline to last available follow-up (2-sided $\alpha = 0.05$). Change from baseline in SNOT-22 (primary outcome) and LK (secondary outcome) scores were analyzed using repeated-measures analysis of variance to assess for differences in score trajectories between the antibiotic and placebo groups. The proportions of participants meeting MCID for improvement in SNOT-22 scores at both postoperative visits as well as the rates of postoperative infection were compared between the groups with z tests for proportions. Participants who developed a postoperative sinus infection required nonblinded, nonrandomized antibiotic treatment and, thus, were included only in analyses comparing postoperative infection rates. Additional exploratory analyses incorporated baseline clinical factors in repeated-measures analysis of covariance to assess for differences in SNOT-22 score trajectories between groups.

The overall between-patient SD of the within-patient change in SNOT-22 score from baseline to the last available follow-up in the present study was 19.9 (similar to 20, the estimate used for sample size calculation) but was significantly different between the antibiotic and placebo groups (F test for variances: $p = 0.009$). Thus, the achieved power was calculated with the SD (15.2) for the group being assessed for noninferiority (placebo). All statistical tests were conducted with JMP Pro version 14 (SAS Institute, Cary, NC).

Results

Participant flow, recruitment, and baseline clinical characteristics

Of the 134 participants enrolled, 45 were excluded before randomization due to surgery cancellation (n = 3), infection identified during ESS (n = 23), stent placement during ESS (n = 3), declining of study medication (n = 12), or other reasons (n = 4) (Fig. 1). Of the remaining 89 participants who were randomized into either the antibiotic (n = 43) or placebo (n = 46) group, 12 were excluded from analysis due to loss to follow-up (n = 2 and 4, respectively), noncompliance with the study medication (n = 3 and 1,

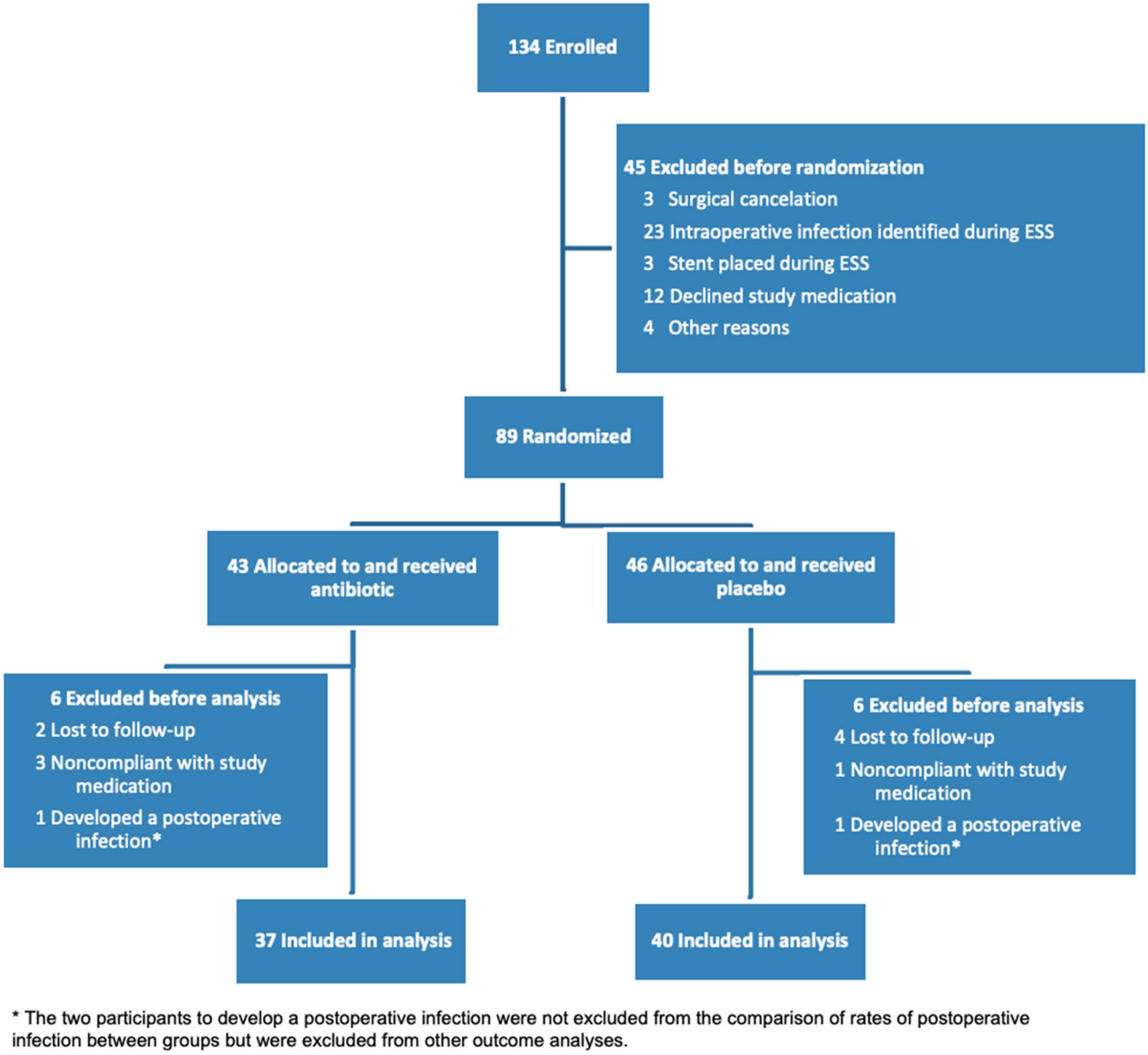

FIGURE 1. CONSORT flow diagram depicting the number of participants included in the enrollment, randomization, allocation, follow-up, and analysis. CONSORT = Consolidated Standards of Reporting Trials; ESS = endoscopic sinus surgery.

respectively), or development of a postoperative sinus infection (n = 1 and 1, respectively). Participants were seen in clinic preoperatively at 4.5 ± 3.7 (range, 0.4-19.4) weeks before ESS. After ESS, participants were followed clinically through 2 serial postoperative visits at 1.3 ± 0.3 (range, 0.7-2.7) weeks and 8.8 ± 3.9 (range, 3.1-28.1) weeks postoperatively. Of the 134 enrolled participants, 57.5% (n = 77) completed the study through the second postoperative visit and were included in the analyses (n = 37 in the antibiotic group, n = 40 in the placebo group). Baseline demographics, clinical characteristics, and culture results of these participants are summarized by group in Table 1.

Participant recruitment occurred from February 2013 through December 2017 (at which point study recruitment was halted due to concern for confounding from unobserved time trends over the nearly 5-year recruitment period), and postoperative visits for study participants were completed in January 2018. Based on the SNOT-22 a priori noninferiority margin of 9, the study achieved 82% power (2-tailed $p < 0.05$).

Outcomes

Based on a SNOT-22 noninferiority threshold of 9, placebo was noninferior to antibiotic prophylaxis with regard to sinonasal-specific QOL ($\beta = 0.18$, 2-tailed $p < 0.05$) (Fig. 2A), the mean change in SNOT-22 score from baseline to the last available follow-up was 22.5 ± 15.2 (95% confidence interval [CI], 17.5-27.5) in the placebo group and 25.4 ± 23.8 (95% CI, 17.5-33.2) in the antibiotic group

TABLE 1. Baseline demographics, clinical characteristics, and culture results*

	All participants (N = 77)	Antibiotic group (N = 37)	Placebo group (N = 40)
Age (mean ± SD), years	44.1 ± 11.5	41.3 ± 10.6	46.7 ± 11.8
Males:females (% female)	50:27 (35%)	23:14 (38%)	27:13 (33%)
Comorbid asthma	39 (51%)	20 (54%)	19 (48%)
History of previous surgery	29 (38%)	13 (35%)	16 (40%)
Nasal polyps	44 (57%)	20 (54%)	24 (60%)
Preoperative CT score	14.6 ± 5.7	14.3 ± 5.1	14.8 ± 6.4
Culture growth	68 (88%)	35 (95%)	33 (83%)
GNR alone	17 (22%)	7 (19%)	10 (25%)
GNR+enterococci	1 (1%)	0 (0%)	1 (3%)
MRSA alone	1 (1%)	0 (0%)	1 (3%)
MSSA alone	10 (13%)	4 (11%)	6 (15%)
MSSA+GNR	5 (6%)	3 (8%)	2 (5%)
MSSA+streptococci	2 (3%)	1 (3%)	1 (3%)
Streptococci alone	5 (6%)	4 (11%)	1 (3%)
Miscellaneous	1 (1%)	1 (3%)	0 (0%)
Normal flora alone	26 (34%)	15 (41%)	11 (28%)

*Data expressed as number (%), unless noted otherwise.
CT = computed tomography; GNR = gram-negative rods; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*; SD = standard deviation.

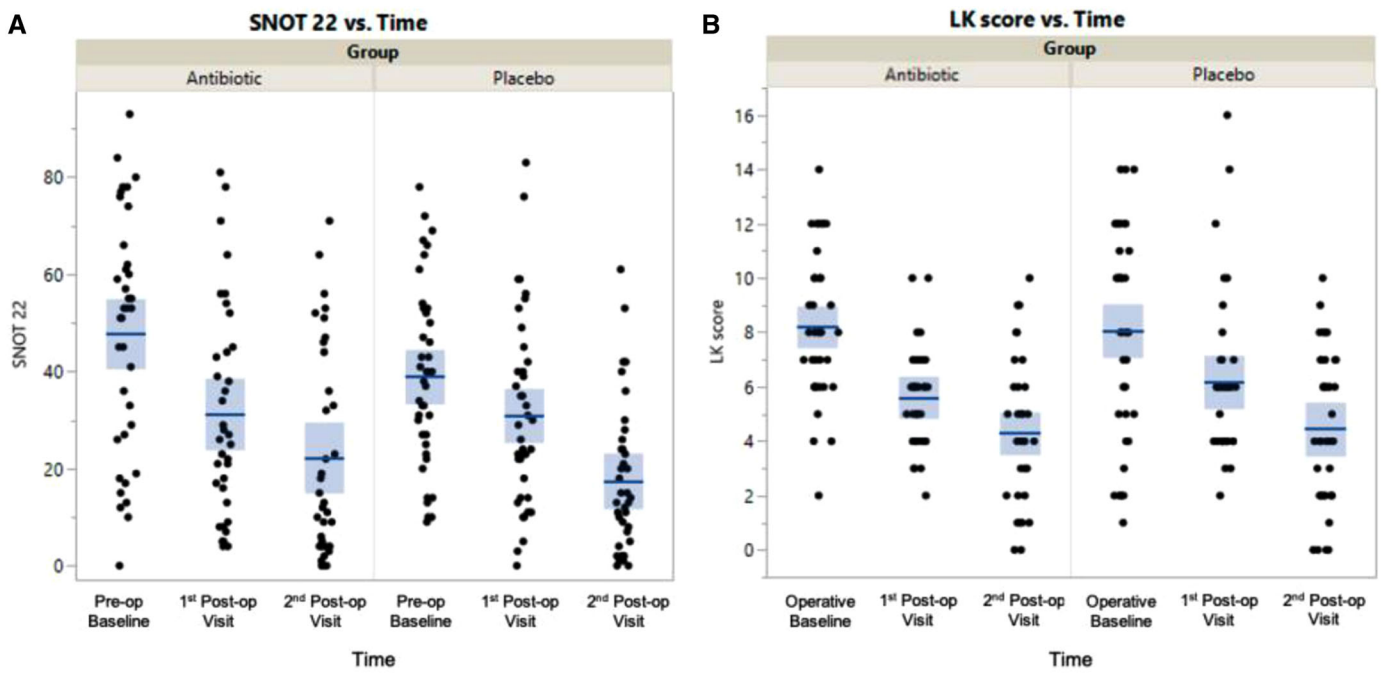

FIGURE 2. The antibiotic group and the placebo group showed similar clinical trajectories as measured by the SNOT-22 score (primary outcome) (A) and the endoscopic LK score (secondary outcome) (B). Shaded regions represent the 95% confidence intervals for the relevant score at each timepoint. LK = Lund-Kennedy; SNOT-22 = 22-item Sino-Nasal Outcome Test.

TABLE 2. Baseline and subsequent SNOT-22 quality of life and LK endoscopic scores*

	Preoperative baseline	Change from baseline to first postoperative visit[a]	Effect size, Cohen's *d* for change from baseline to first postoperative visit	Change from baseline to second postoperative visit[a]	Effect size, Cohen's *d* for change from baseline to second postoperative visit
SNOT-22 scores					
All patients	43.5 ± 21.6 (77)	11.9 ± 22.3 (76)	0.61 (0.28 to 0.93)	23.9 ± 19.9 (74)	1.20 (0.86 to 1.54)
Antibiotic group	47.7 ± 24.4 (37)	16.0 ± 23.2 (36)	0.82 (0.35 to 1.28)	25.4 ± 23.8 (37)	1.26 (0.78 to 1.73)
Placebo group	39.7 ± 18.1 (40)	8.3 ± 21.1 (40)	0.40 (−0.05 to 0.83)	22.5 ± 15.2 (37)	1.14 (0.68 to 1.61)
LK scores					
All patients	8.3 ± 3.2 (77)	2.4 ± 3.4 (77)	0.83 (0.51 to 1.16)	4.0 ± 3.2 (74)	1.39 (1.05 to 1.74)
Antibiotic group	8.3 ± 2.7 (37)	2.7 ± 2.7 (37)	0.91 (0.45 to 1.37)	3.9 ± 3.4 (36)	1.37 (0.90 to 1.84)
Placebo group	8.3 ± 3.7 (40)	2.1 ± 3.9 (40)	0.66 (0.22 to 1.10)	4.0 ± 2.9 (39)	1.27 (0.82 to 1.72)

*Data expressed as either mean ± standard deviation (N) or as Cohen's *d* (95% confidence interval).
[a]For SNOT-22 score change from preoperative baseline to postoperative visit, positive values represent improvement in quality of life; that is, the greater the positive value, the greater the quality of life improvement at follow-up relative to baseline.
[b]For LK score change from operative baseline to postoperative visit, positive values represent improvement in endoscopic grade; that is, the greater the positive value, the greater the endoscopic improvement at follow-up relative to baseline.
CI = confidence interval; LK = Lund-Kennedy; SNOT-22 = 22-item Sino-Nasal Outcome Test.

TABLE 3. Results of exploratory analyses for binary covariates and SNOT-22 quality of life scores and LK endoscopic score trajectories

Covariate	SNOT-22 scores			LK scores		
	Effect size[a] (Cohen's *d*)	95% CI	*p* value	Effect size[a] (Cohen's *d*)	95% CI	*p* value
Asthma	0.17	−0.40 to 0.74	0.80	0.02	−0.55 to 0.60	0.98
Nasal polyps	0.27	−0.28 to 0.82	0.48	0.12	−0.43 to 0.68	0.29
Previous ESS	0.39	−0.27 to 1.05	0.80	0.03	−0.61 to 0.68	0.66
Culture growth	0.23	−0.30 to 0.76	0.89	0.13	−0.27 to 0.53	0.82

[a]Adjusted effect size at last available follow-up.
CI = confidence interval; ESS = endoscopic sinus surgery; LK = Lund-Kennedy; SNOT-22 = 22-item Sino-Nasal Outcome Test.

(Table 2 and Fig. 2A). This intention-to-treat analysis included 1 participant from the antibiotic group who only completed the second postoperative SNOT-22 survey and 3 participants from the placebo group who only completed the first postoperative SNOT-22 survey. The proportions of participants meeting MCID for improvement in SNOT-22 score from baseline did not differ significantly between the antibiotic and placebo groups at either the first (21 of 36 [58.3%] vs 21 of 40 [52.5%], respectively; z score = 0.511; $p = 0.61$) or second (30 of 37 [81.1%] vs 32 of 37 [86.5%], respectively; z score = −0.631; $p = 0.53$) postoperative visit.

There were no significant differences between the antibiotic and placebo groups in LK score trajectories over time (Cohen's d [95% CI], 1.26 [0.79-1.73] vs 1.06 [0.61-1.28], respectively; $p = 0.63$) (Table 2 and Fig. 2B). There was no significant difference between the antibiotic and placebo groups in the postoperative sinus infection rate (1 of 38 [2.6%] vs 1 of 41 [2.4%], respectively; relative risk of infection in the antibiotic group = 1.08; z score = 0.054; $p = 0.96$).

On exploratory analyses, there were no significant effects of comorbid asthma, presence of nasal polyps, history of ESS, or operative culture growth on the SNOT-22 or LK score trajectories over time (Cohen's d and p values in Table 3 and Fig. 3), nor was there a significant effect of the preoperative Lund-Mackay CT score on the SNOT-22 (adjusted $r^2 = -0.006$; $p = 0.70$) or LK ($r^2 = 0.006$; $p = 0.19$) score trajectories over time.

Harms

No adverse events occurred in either group. The rate of diarrhea was significantly higher in the antibiotic group compared with the placebo group (9 of 37 [24.3%] vs 1 of 40 [2.5%], respectively; relative risk = 10.8; z score = 2.32; $p = 0.02$).

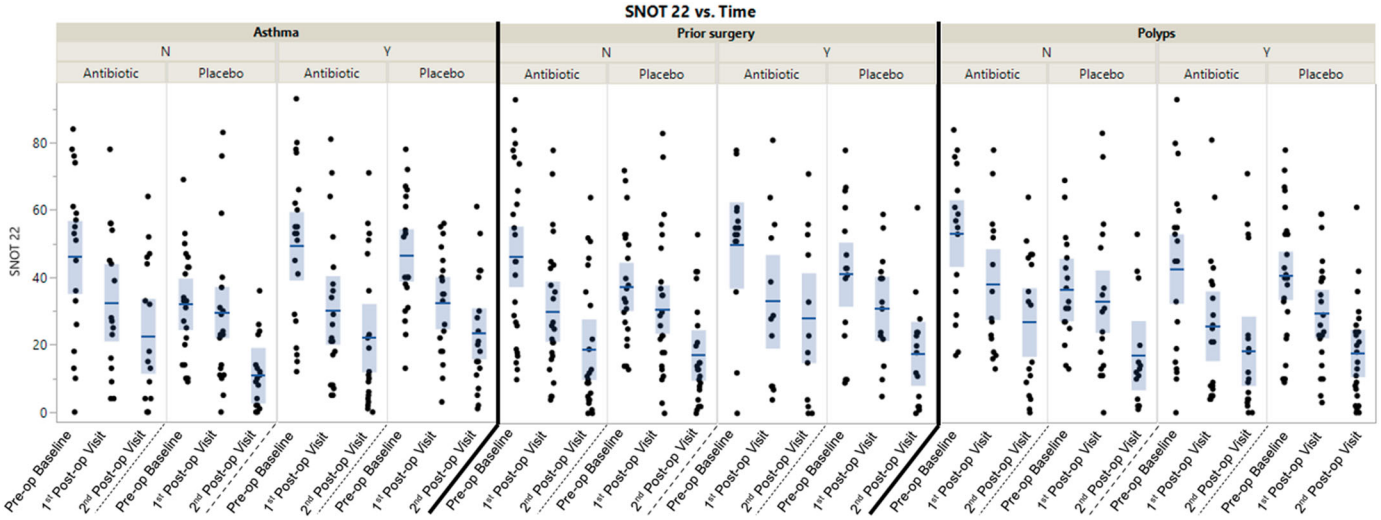

FIGURE 3. On exploratory analyses, there were no significant effects of comorbid asthma, history of prior sinus surgery, or presence of nasal polyps on the SNOT-22 score trajectories over time in the antibiotic group or placebo group. Shaded regions represent the 95% confidence intervals for SNOT-22 scores at each time point. N = no, the participants do not have a history of asthma, prior ESS, or nasal polyps; SNOT-22 = 22-item Sino-Nasal Outcome Test; Y = yes, the participants do have a history of asthma, prior ESS, or nasal polyps.

Discussion

The majority of otolaryngologists report prescribing prophylactic postoperative antibiotics for patients undergoing ESS for medically refractory CRS (from 62.3%[3] to 86.8%[15]), most often citing a need to reduce the risk of postoperative infection (75.6%).[3] Although this is a commonly held belief, there is a paucity of data concerning the incidence of postoperative sinus infections, which may range from 2.5% (2 of 79 in the present study) to 14.9% (30 of 202 in a previously reported study).[7] In the current randomized, double-blind, placebo-controlled, noninferiority clinical trial, placebo was found to be noninferior to postoperative antibiotic prophylaxis with 1 week of amoxicillin-clavulanate in terms of short-term (at an average of 9 weeks postoperatively) sinonasal-specific QOL, and there was no significant difference in the rate of postoperative sinus infections between groups. Although the current study is statistically underpowered with an achieved power of 82% to comment conclusively on noninferiority, the results are consistent throughout the study: The administration of postoperative prophylactic antibiotics or placebo had no significant effect on participants' postoperative sinonasal-specific QOL or endoscopic scores, regardless of the severity of their preoperative imaging or whether they had nasal polyps, asthma, a history of ESS, or growth on their operative cultures. Of note, 88% (N = 68) of the operative cultures in this study demonstrated growth, with 55% (N = 42) demonstrating growth beyond normal flora alone, even in the absence of an active sinus infection evidenced on intraoperative sinonasal endoscopy. These rates of sinonasal culture growth reflect that the sinonasal cavity is known to be nonsterile in both healthy and diseased states, and microbiota are readily identified from samples of CRS patients undergoing ESS by culture or culture-independent techniques.[16]

Although there were no significant differences between the groups in QOL outcomes (including the likelihood of reaching MCID) or postoperative sinus infection rates, use of antibiotic significantly increased the risk of diarrhea, with a 10-fold higher rate of diarrhea in the antibiotic group compared with the placebo group. Together, these findings suggest avoiding antibiotic prophylaxis may decrease risk for patients without negatively affecting their surgical outcomes.

To our knowledge, the results of this trial are the first to suggest the noninferiority of withholding postoperative prophylactic antibiotics (vs giving them) in patients with no intraoperative evidence of active infection at the time of ESS. There are, however, several randomized, controlled trials that assessed whether postoperative antibiotics are superior to withholding antibiotics.[7–10] The majority of those earlier studies did not find a significant difference in short-term outcomes after ESS whether placebo was administered[7,8] or no-antibiotic control groups were used.[9] One trial, however, showed transiently greater improvements in symptoms (specifically regarding nasal obstruction and drainage) and endoscopic scores during the first 2 weeks post-ESS in the antibiotic group (receiving twice-daily amoxicillin-clavulanate 625 mg for 2 weeks postoperatively) relative to the placebo group.[10] Nevertheless, this observed effect of improved early outcomes was short-lived. By the third and fourth weeks postoperatively, there were no significant differences between the groups for either symptom or endoscopic scores.[10] In the present study we followed participants to an average of 9 weeks postoperatively yet found no significant difference between the groups at either the 1- or 9-week postoperative visit.

These aforementioned trials also either did not use well-validated patient-reported outcome measures (but rather subjective symptom records/scores[7,9,10]) or used nonstandard postoperative antibiotic durations (eg, 3 weeks[9] or 4 weeks[8]). The only trial to use a validated instrument for patient-reported outcomes showed no significant differences between its antibiotic group and placebo group, based on a validated Chinese translation[17] of the validated 31-item Rhinosinusitis Outcome Measure[18] or on nasal endoscopy findings at 8 weeks postoperatively.[8]

Previous trial results[7,9,10] have been pooled for a meta-analysis, which showed no significant differences in postoperative infection rates, symptom scores, or endoscopic scores due to post-ESS antibiotic prophylaxis.[2] A recent review study on perioperative antibiotic use in otolaryngology concluded that the current evidence does not support the use of routine antibiotic prophylaxis for ESS.[19] Despite these findings, a great deal of variability exists in perioperative antibiotic practice patterns between surgeons performing ESS and across practice sites,[20] as post-ESS antibiotic prescribing is generally still based on surgeon discretion.[3,21]

High rates of postoperative prophylactic antibiotic prescription after ESS[3,15] persist despite evidence against their use as well as national and international guidelines advising against such use. Guidelines for antibiotic prophylaxis in surgery developed jointly by the American Society of Health-System Pharmacists, Infectious Diseases Society of America, Surgical Infection Society, and Society for Healthcare Epidemiology of America do not recommend any prophylactic antibiotics for uncomplicated ESS (either pre- or postoperatively).[22] The World Health Organization recommends against continuing antibiotic prophylaxis postoperatively for any type of surgery, stating: "The panel recommends against the prolongation of [surgical antibiotic prophylaxis] administration after completion of the operation for the purpose of preventing [surgical site infections] (Strong recommendation/moderate quality of evidence)."[23] The US Centers for Disease Control and Prevention also strongly recommend against postoperative antibiotic prophylaxis, stating: "In clean and clean-contaminated procedures, do not administer additional prophylactic antimicrobial agent doses after the surgical incision is closed in the operating room, even in the presence of a drain (Category IA—strong recommendation; high-quality evidence)."[24] These recent national and international guidelines recommend a single dose of prophylactic antibiotic administered immediately before surgery for some types of surgery but do not recommend any routine postoperative antibiotic prophylaxis. Furthermore, as antibiotics are the leading cause of medication-related litigation, the potential medicolegal implications of inappropriate antibiotic use offer a further deterrent to their unnecessary prescription.[25]

Postoperative prophylactic antibiotics may be considered when nasal packing is placed due to the concern for toxic shock syndrome. Although a review of 10 randomized control trials and a retrospective cohort failed to show an increase in local infection rates when nasal packs or splints were placed during surgery, available studies were underpowered to comment on the rare risk of toxic shock syndrome.[19] The current trial excluded patients in whom packing was placed. Our study also excluded patients with immunodeficiency, pregnancy, and cystic fibrosis, and thus the results are not generalizable to such patients.

The major limitation of the present trial is that it achieved a power of 82%. This achieved power is due to a smaller proportion (57.5%) of enrolled participants completing the study than anticipated and recruitment being halted before reaching the goal set in the power calculation. Although the low enrollment numbers are in part due to the restrictive exclusion criteria employed, we also found reluctance from patients to participate in a study that may lead to their unnecessary use of postoperative antibiotics. Many patients informed of the option to participate in this study declined to participate, instead preferring to forego antibiotics with certainty after surgery. This preference expressed by many declining patients may reflect changing public opinion regarding antibiotic usage.[26]

Additional limitations of the present trial include that these results pertain to a single antibiotic and duration of treatment, thereby limiting their generalizability to other potential antibiotic selections and durations. The addition of clavulanate to amoxicillin has been shown in a meta-analysis to more than double the incidence of antibiotic-associated diarrhea (8.1% with amoxicillin alone vs 19.8% for amoxicillin-clavulanate),[27] and thus selection of amoxicillin alone may have decreased the observed rates of diarrhea. Also, although no adverse events occurred, even short-term oral antibiotic courses carry well-established risks beyond the observed side effect of diarrhea, including the selection of resistant bacteria, antibiotic-related allergic reactions, and *Clostridioides difficile*–associated infections.[6] A larger trial may have identified such antibiotic-related adverse events. Furthermore, multiple analyses were conducted for secondary and exploratory analyses, and these findings are not intended to guide clinical practice.

Conclusion

Currently, prophylactic antibiotic use after ESS varies greatly among surgeons.[3,15] However, use of prophylactic antibiotics should only be considered with the knowledge of benefits vs known risks (eg, diarrhea). In the present study we found no evidence of benefit in the antibiotic group, yet the group had a 10-fold higher rate of diarrhea than the placebo group. Our findings support national and international guidelines that recommend against postoperative prophylactic antibiotics after ESS.

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