

ORIGINAL RESEARCH

Microbiomics of irrigation with xylitol or *Lactococcus lactis* in chronic rhinosinusitis

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Abstract

Objective: Topical sinonasal rinse therapies may alter the local microbiome and improve disease control in chronic rhinosinusitis (CRS). The objective of this study was to examine microbiome changes in post-surgical CRS patients when rinsing with commercially available products containing xylitol or *Lactococcus lactis*.

Methods: A crossover-type protocol with a washout period was designed. Swab samples from anterior ethmoid cavities of CRS patients were collected prospectively at baseline. Subjects were provided packets containing either *L. lactis* W136 or xylitol in non-blinded fashion and instructed to add it to their rinse bottles daily for 28 days, after which another swab was taken. A saline wash-out period was completed and a third swab taken. A final 28-day regimen of the opposite product was followed by a final swab. DNA extraction and sequencing of the 16S rRNA gene allowed for global microbiome analysis.

Results: We enrolled 25 subjects with CRS and 10 controls resulting in 70 adequate samples. Increased detection of *Lactococcus* was observed after use of *L. lactis*. No significant trends in alpha or beta diversity as a result of treatment were observed. SNOT-22 score did not change significantly following treatment with xylitol, *L. lactis*, or saline.

Conclusion: We did not detect any major clinical or microbiome-level effect due to treatment with two topical rinse products. Further research is needed to elucidate their clinical utility and possible probiotic effect.

Level of Evidence: 3.

KEYWORDS

adult rhinology, quality of life

1 | INTRODUCTION

Dysbiosis, or pathologic change in the microbial community of a host environment, may help explain the pathophysiology of chronic

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rhinosinusitis (CRS). The sinonasal mucosal spaces are colonized with a variety of commensal organisms including anaerobic and aerobic bacteria as well as fungi. Recent studies have demonstrated that multiple markers of community diversity are decreased in CRS.¹ Reduced diversity may help initiate, perpetuate, or modify treatment outcomes in CRS, according to the “microbiome hypothesis.”²

Topical therapies are a mainstay of clinical treatment of CRS.³ Low-pressure, high-volume saline is commonly used to irrigate the sinonasal cavities, deliver topical medications, or both. Available in the United States and Canada since 2018, *Lactococcus lactis* W136 (ProbioRinse) is marketed as a probiotic and can be purchased in packet form for topical rinse application in the nose and sinuses.⁴ Cho et al co-cultured different *Pseudomonas aeruginosa* strains with this commercial *L. lactis*.⁵ They found no effect on 4 strains, a modest inhibitory effect on one strain, and a modest proliferative effect on one. Xylitol, a sugar alcohol widely used as an artificial sweetener, is the main ingredient in another over-the-counter product in packet form (Xlear). Use of xylitol improved Sino-Nasal Outcome Test-22 (SNOT-22) scores and increased nasal nitric oxide and inducible nitric oxide synthase significantly compared to saline.⁶ There is evidence xylitol inhibits growth of several common pathogens of the upper aerodigestive tract⁷ and may prevent dental caries, although quality of evidence is low.⁸

Whereas culture-based methods may capture only a few culturable species, 16S rRNA amplicon sequencing can detect more bacterial taxa in greater depth. A form of next-generation sequencing, 16S rRNA sequencing is culture-independent and non-targeted, using primers that amplify the 16S rRNA gene, which is conserved across bacteria. Recent studies have examined the CRS microbiome via 16S sequencing. Merkley et al demonstrated that treatment of acute exacerbations of CRS with antibiotics increased diversity and decreased total bacteria.⁹ Outcomes in sinus surgery improve with increased microbial diversity detected at the time of surgery.¹⁰ CRS may result from a compounded effect of dysbiosis and host hyperresponsiveness, and the role of the microbiome is complex.¹¹

On their respective websites, Xlear states that xylitol “works against bacteria” to improve sinus health,¹² and ProbioRinse is described as “the first sinus irrigation solution with probiotic designed for topical administration.”¹³ In this study, we sought to characterize the paranasal sinus microbiome changes of subjects with CRS following 4 weeks of irrigation with either *L. lactis* or xylitol. We enrolled subjects prospectively in non-blinded, pseudorandomized fashion.

2 | MATERIALS AND METHODS

Institutional Review Board approval was gained from the University of Rochester’s Research Subjects Review Board. Subjects were identified via review of clinical schedules of attending physicians in the Department of Otolaryngology Head and Neck Surgery. Subjects were recruited via telephone call or clinical visits. For inclusion, subjects were 18 years old or older, with a diagnosis of CRS and a history

of endoscopic sinus surgery consisting of at least bilateral maxillary anastomies and anterior ethmoidectomies. CRS subjects could be with or without polyposis. Surgery must have been at least 3 months prior to enrollment. Subjects were eligible if they were using a sinonasal rinse bottle with saline alone or saline plus steroid, at least once daily. Subjects were excluded if they had taken an antibiotic or systemic steroid in the previous 4 weeks, whether for apparent sinus infection or otherwise. If they required antibiotics or systemic steroids at any point, their participation in the study was stopped. Data collected prior to dropout was collected, and they were eligible to re-enroll after 4 weeks. If re-enrolled, data from the previous enrollment was discarded. Further exclusion criteria included hypersensitivity to study products, immunosuppression, decisional impairment, incarceration, and non-English-speaking status. Written informed consent was signed for all subjects. Baseline medical regimens were not changed at any point during participation.

Each enrollment comprised up to 4 study visits. At each visit, subjects completed a SNOT-22 symptom inventory questionnaire and verified ongoing inclusion eligibility. The study design was as follows. At the first visit, subjects were placed in one of two arms of the study. Subjects were alternated to arm 1 or 2 as they enrolled to ensure equal distributions. Each arm was a mirror image of the other, in a crossover-study fashion. Arm 1 had subjects use xylitol for 4 weeks, followed by a saline washout period of at least 4 weeks, followed by use of *L. lactis* for 4 weeks. Arm 2 reversed the order of the products used but was otherwise identical. Therefore, subjects could complete up to 3 phases of a given arm (xylitol, saline, and *L. lactis*), requiring 4 visits (one at enrollment, and one at conclusion of each phase). At each visit, subjects underwent endoscopically-guided swabs of their anterior ethmoid cavities bilaterally. Swabs (FLOQSwabs; COPAN Flock Technologies, Murrieta, California) were sheathed in sterile tubing until deployment into the ethmoid cavity to prevent contamination by nasal skin and mucosa. Subjects were then provided with a one-month supply of xylitol (Xlear, Xlear, Inc., American Fork, Utah) or *L. lactis* (ProbioRinse, ProbioNase Therapies, Montreal, Quebec, Canada) packets and instructed to use one packet daily. All subjects used high-volume, low-pressure sinus rinse bottles (NeilMed Pharmaceuticals, Inc., Santa Rosa, California) with sterile water to dissolve and deliver the provided packets. They were provided with, and instructed to use, a new rinse bottle at each visit. Subjects kept a diary to verify acceptable use of the products. They were instructed to make no other changes to their rinse regimen, including performing their usual rinses beyond once a day and adding steroid if already doing so. Subjects were seen 28 ± 3 days (to allow scheduling flexibility) following their first visit. At this second visit, they were instructed to stop the study product and return to their baseline rinse regimen. Following a minimum of 28 days, subjects returned for a third visit and were given a one-month supply of the opposite product for daily use. Finally, 28 ± 3 days later, the fourth and final visit occurred and subjects were discharged from the study. A flowchart summarizing the two arms is given in Figure 1A.

Healthy control subjects were recruited as well. Inclusion criteria for controls were: no history of nasal or sinus surgery, no history of

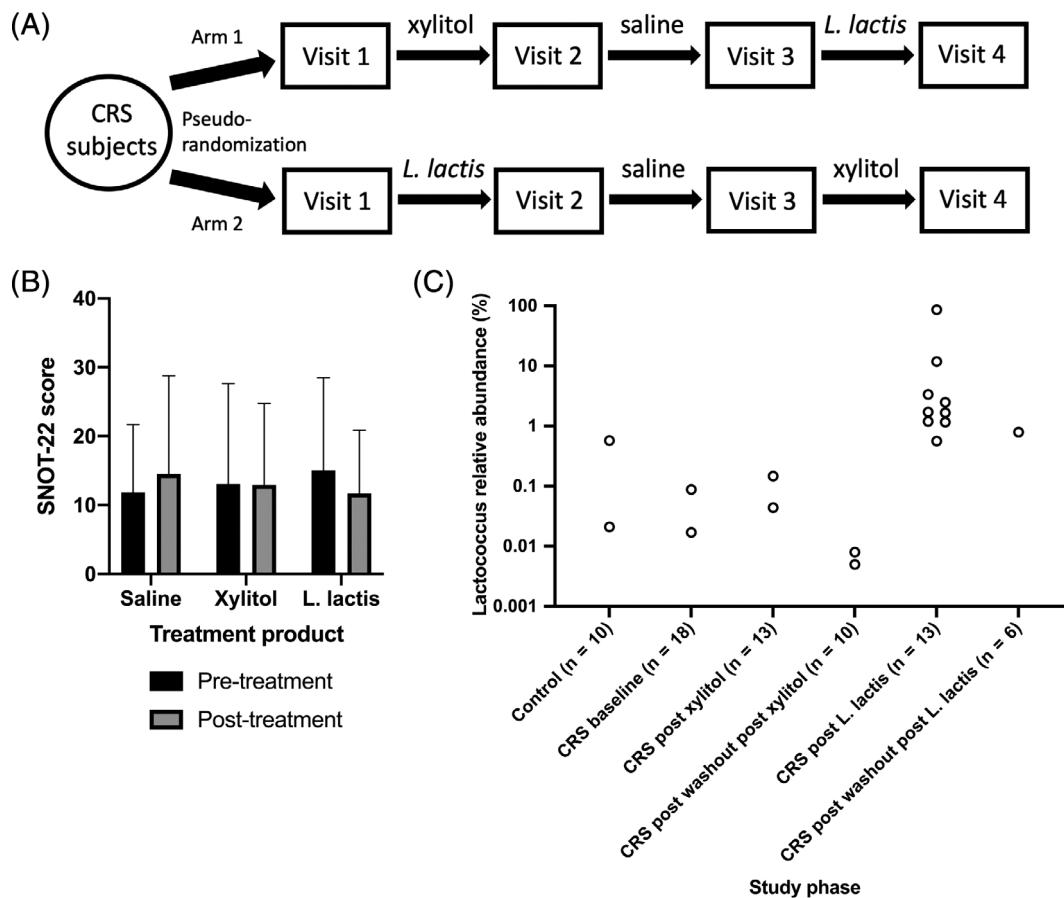


FIGURE 1 A, Flowsheet depicting the two arms of the study and the four study visits. B, Sino-nasal Outcome Test (SNOT-22) scores before and after use of study rinse products. Error bars represent SD. C, Relative abundance of *Lactococcus* by study phase. In samples where no *Lactococcus* was detected, no data point is shown. Y-axis is given on a logarithmic scale

CRS or other sinonasal condition, SNOT-22 score less than 30, age 18 or older, reported 5 or fewer upper respiratory infections per year. Exclusion criteria were the same as for experimental subjects. Controls underwent a one-time swab of the middle meatus with the same technique as described above.

The swabs were immediately placed in 1 mL UV-treated sterile phosphate buffered saline and then in a 4°C refrigerator. Within 48 hours they were transferred to a -80°C freezer. For consistency only the right-sided samples were used.

Total genomic DNA was extracted and 16S ribosomal RNA was amplified with primers targeting the V1-V3 hypervariable regions and sequenced at the University of Rochester Genomics Research Center. Bioinformatics processing occurred in QIIME2¹⁴ with taxonomic assignments via GreenGenes.¹⁵ Further details are given in the Supplemental Methods.

Statistical analysis occurred in QIIME2 and GraphPad Prism (GraphPad, La Jolla, California). Comparisons between experimental groups were made using Fisher's exact test and paired Student 2-sample t test with two tails unless specified. Comparisons among multiple groups were with 1-way analysis of variance (ANOVA). We generated alpha diversity and beta diversity indices from validated QIIME scripts.

3 | RESULTS

We enrolled 25 subjects with CRS. Two subjects who required antibiotics re-enrolled at a later date once re-eligible, for a total of 27 enrollments. The data from the first enrollments for those two subjects was discarded. 17 subjects completed all 4 subject visits. The remaining 10 enrollments were suspended due to requiring antibiotics and/or systemic steroids for a variety of reasons (CRS exacerbation, n = 3; upper respiratory infection symptoms, n = 2; dental procedure requiring oral antibiotics, n = 2; extremity injury, n = 1; other illness or no-show, n = 2). Data and samples collected prior to initiation of antibiotics or steroids were included. We enrolled 10 control subjects without CRS. Demographics with statistical comparisons are given in Table 1.

There were no major or minor complications attributed to use of any of the study products. There were no cases of allergy or intolerance. While there were cases of exacerbations of CRS symptoms, it was felt these were within the normal pattern of these patients' recent histories. All subjects used the provided rinse product at least 21 days based on history and diary review. The mean number of days of product use was not significantly different ($P = .36$). Days of use for xylitol was 27.9 (95% CI, 26.9-28.9) and for *L. lactis* was 27.2 (95% CI,

TABLE 1 Demographics of study subjects

	Control (n = 10)	CRS, all (n = 25)	CRS, arm 1 (n = 13)	CRS, arm 2 (n = 12)	P value, control vs CRS	P value, CRS arm 1 vs arm 2
Mean age in years (95% CI)	25.2 (22.2-28.2)	48.6 (43.3-53.9)	49.8 (42.3-57.4)	47.3 (39.6-55.1)	<.001	.65
Female, n (%)	6 (60)	16 (64)	8 (62)	8 (67)	.82	.79
Diabetes, n (%)	0 (0)	2 (8)	0 (0)	2 (0.17)	.36	.12
Never smoker, n (%)	9 (90)	19 (76)	10 (77)	9 (75)	.35	.91
Polyposis, n (%)	0 (0)	22 (88)	11 (85)	11 (92)	<.001	.59
Visit 1 SNOT-22 score (95% CI)	8.5 (4.2-12.8)	15.3 (9.8-20.8)	11.3 (5.5-17.1)	19.6 (10.4-28.8)	.03 (one-tailed)	.15

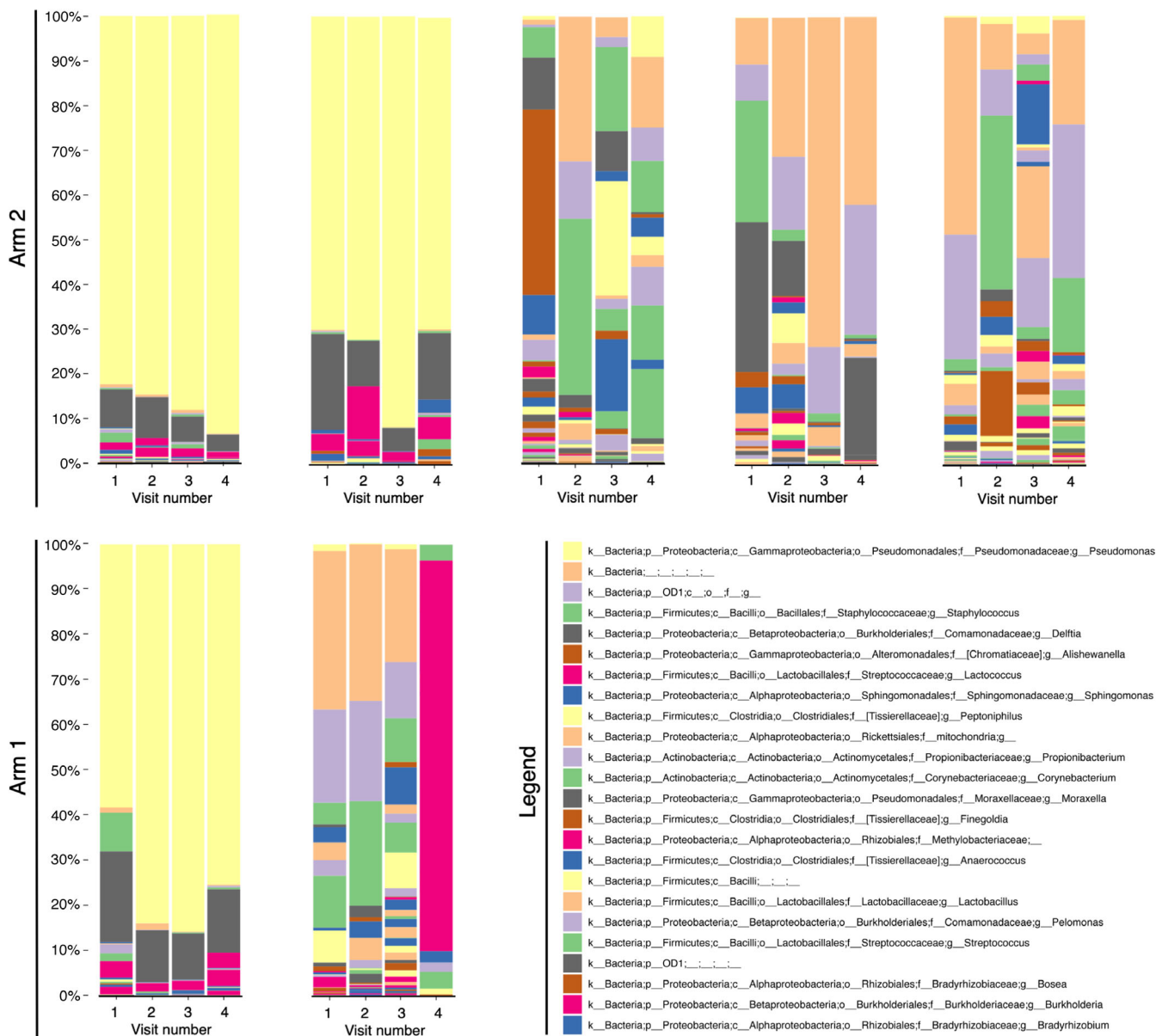


FIGURE 2 Graphical representation of the operational taxonomic units, with kingdom, phylum, class, order, family, and genus as indicated, from enrolled subjects that completed all 4 study visits. For clarity, legend was truncated at 24 labels; the full legend is available in the supplemental material. Each group of vertical bars represents one subject across 4 visits

26.2-28.2). Saline washout was at least 25 days for all subjects, with a 28 day washout period being typical.

The demographics of the enrolled participants are detailed in Figure 1A. Average SNOT-22 at baseline for CRS subjects was 15.3 (95% CI, 5.5-20.8). We did not find any significant change in SNOT-22 associated with any of the study phases. The average SNOT-22 score at each visit is depicted in Figure 1B. We observed a 3.4 point improvement ($P = .07$, 95% CI -4.2 to 10.9) in SNOT-22 with use of *L. lactis* that did not reach statistical significance.

Microbiome analysis was limited by failure to recover and amplify adequate DNA in low biomass samples or to reach sufficient reads per sample. After removing those samples for quality control, 70 samples were successfully analyzed.

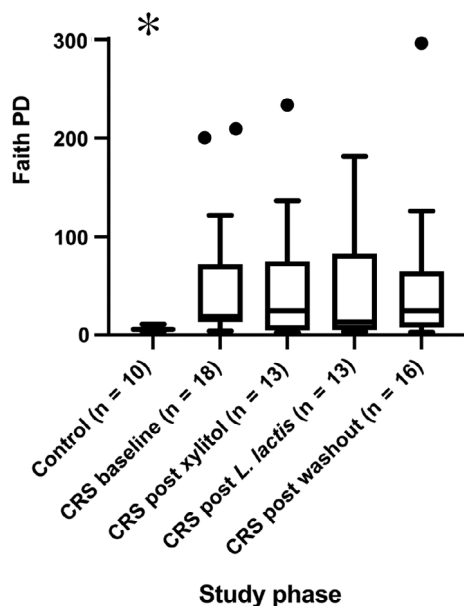


FIGURE 3 Alpha diversity (Faith PD) by study phase in standard Tukey box-and-whisker plot. Boxes represent interquartile ranges. Middle line represents the median. Whiskers represent “maximum” or “minimum” with outliers beyond 150% of interquartile range depicted as dots. Asterisk represents significantly ($P < .05$) different from each other group individually

We examined the detection of *Lactococcus* as a function of study phase. *Lactococcus* spp. reached genus level identification. *Lactococcus* was identified in 18 of 70 samples. It was found in at least one sample from each group, suggesting *Lactococcus* spp., whether *L. lactis* or otherwise, occur naturally in some individuals' sinus cavities. It was found in 9 of 13 (69%) samples taken at the end of use of *L. lactis*. It was found in only 1 of 6 (17%) samples after a subsequent saline washout, and that sample actually came from a subject for whom no *Lactococcus* was seen immediately after *L. lactis* irrigations. We also detected *Lactococcus* in 2 of 13 (15%) samples taken from subjects who had just completed the xylitol phase. It was found in 2 of 10 (20%) samples after a washout after xylitol, and 2 of 10 (20%) control samples. Figure 1C depicts a graphical summary of the proportional abundance of *Lactococcus* in each sample. The relative risk of finding *Lactococcus* after use of *L. lactis* compared to xylitol was 4.5 (95% CI, 1.5-16.6, $P = .008$, one-tailed). The relative risk was also statistically significant when compared to all other CRS samples at 4.6 (95% CI, 2.1-10.0, $P = .0003$).

Of those who completed all 4 visits, 7 subjects had a complete set of samples that adequately amplified and sequenced. A graphical breakdown of the microbiome constituents of those 7 subjects is in Figure 2. The results did not reveal a clear pattern in terms of species present relative to study phase. Rather, overall compositions appeared to be driven largely by individual differences rather than treatment.

We examined pooled results by study phase. Data were pooled from all subjects who completed 4 weeks of a given rinse: *L. lactis*, xylitol, or saline. We also examined control results. We compared alpha diversity in the form of Faith's phylogenetic diversity (PD) across these groups. There was a significant difference ($P = .007$) between the control results (6.4, 95% CI 1.5-7.9) and the CRS baseline results (54.0, 95% CI 30.1-84.1). There was also a significant difference between control and CRS at each phase: compared to use of *L. lactis* (46.8, 95% CI 29.7-76.5, $P = .02$), xylitol (50.0, 95% CI 12.8-87.2, $P = .04$), and saline (49.7, 95% CI 36.2-86.0, $P = .03$). Among the CRS subjects, alpha diversity did not significantly change for any of the phases (ANOVA, $P = .99$) (Figure 3).

We used a Weighted UniFrac metric to investigate beta diversity plots across study phases. A representative principal component analysis (PCoA) plot is given in Figure 4. There is a clear clustering of

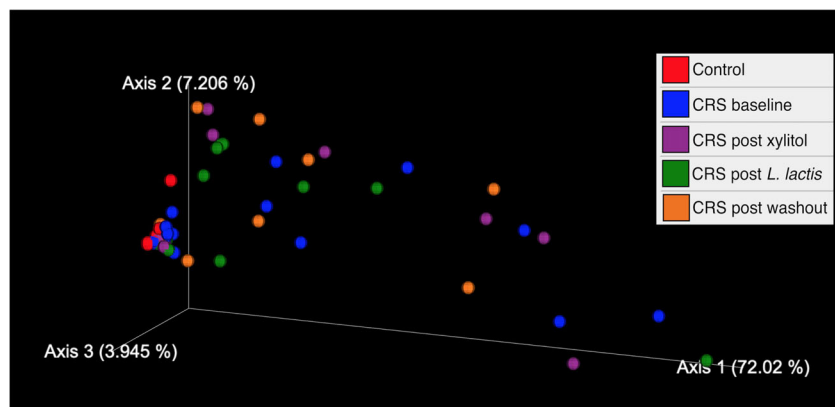


FIGURE 4 Beta-diversity ordination with 3 axes. Principal component analysis based on Weighted UniFrac metric

control subjects primarily along axis 1. Subjects with CRS varied more along axis 1. Study phase did not clearly cluster along any axis.

4 | DISCUSSION

We sought to evaluate bacterial community changes associated with use of relatively novel sinonasal rinse products in CRS. We included control subjects without CRS to contextualize our results. Healthy subjects did have significantly different findings from patients with disease, as would be expected. Their SNOT-22 scores were substantially lower, with the note that score over 30 was grounds for exclusion. CRS subjects' scores were within a range seen in the literature in postoperative settings.¹⁶

SNOT-22 has a minimal clinically important difference of about 9 points for CRS.¹⁷ Study participants did not achieve significant changes in SNOT-22 over the study phases. Although use of *L. lactis* had a small effect of 3.4 points on SNOT-22, this change was not statistically or clinically significant. There are multiple plausible explanations for this negative result. Likely most subjects were already in a “steady state” having had surgery and using daily rinses, and their sinonasal symptoms may have had little room to improve. We also captured changes after 4 weeks of daily product use, and more prolonged or frequent use could yield different results. Although saline rinses with or without steroid have become accepted clinical management tools for chronic rhinosinusitis, other products have not been shown to have the same utility. The mechanical action of saline alone probably accounts for much of the effect.

Weighted UniFrac mapping of the 70 subject samples did result in a distribution of results along axis 1, suggesting between-group variability, but this finding was driven by the clustering of control subjects. Otherwise, study phase did not appear to generate clustering; that is, variation in microbiome across our study, or beta diversity, is not explained by use of the study products. Alpha diversity was highly variable among study subjects and higher than controls. This result was somewhat surprising. Biswas et al found decreased diversity in CRS compared to controls.¹⁸ A similar finding is noted by Abreu et al.¹⁹ However, in both studies, samples were taken at the time of sinus surgery, rather than in the distant postoperative period as ours were. Endoscopic sinus surgery has been shown to increase sinonasal microbiome richness.²⁰ Access of airflow, saline rinses, and other paranasal sinus niche inhabitants to the postoperative ethmoid cavity may allow increased phylogenetic diversity compared to the middle meatus of healthy individuals. Similar to prior studies, diversity varied highly among CRS subjects.²¹ We also cannot rule out that small sample size contributed to this result.

Alpha diversity did not correlate with study phase. While well tolerated, use of xylitol and *L. lactis* did not improve the richness of the bacterial community in our subjects. *L. lactis* is a live organism that is generally recognized as safe by the United States Food and Drug Administration. In preclinical studies, the organism was well tolerated by sinus epithelium, and at selected concentrations induced production of the anti-inflammatory factor IL-10 by peripheral blood mononuclear cells.²² An early clinical study has been reported to show improvement in symptom

and endoscopic scores with twice-daily use of *L. lactis* for 14 days in subjects who had failed endoscopic sinus surgery, and hopefully more clinical information will be forthcoming.⁴ It is possible that the microbiome of patients who did not respond well to sinus surgery may be more favorably altered by this product. Twice daily use could also have an added effect over the findings in our study. ProbioRinse is advertised to “restore a balanced nasal and sinus bacterial flora,” and further investigation is needed to support this statement.¹³ We did detect increased *Lactococcus* in samples from subjects who had just used that product, as would be expected, at a high (69%) but not 100% rate. Relative abundance of the bacteria was variable among those subjects as well. This suggests that *Lactococcus* may take up residence in the nose and sinuses of some patients but not others. After saline washout, *Lactococcus* detection dropped to 17%. Although only 6 subjects were available for this stage of analysis and larger numbers would be desirable, this suggests *Lactococcus* may not durably join already-established bacterial communities, but rather be transiently introduced by rinsing.

Xylitol is the main ingredient in Xlear sinus rinse packets. To our knowledge, there have been two clinical studies of xylitol in chronic rhinosinusitis. Both were small studies but reported modest improvements in SNOT-20²³ or SNOT-22⁶ over saline. Those studies used 12 g of xylitol in 240 mL of saline, which is double the amount in a Xlear packet. The higher dose may account for the positive effect, or patient or other factors may play a role. Xylitol has been investigated for its possible benefits at other body sites, and use in the nose and sinuses may be considered further in future studies.⁷

Limitations of this study include the small sample size. Due to the nature of microbiome data, formal power calculations were not used to guide enrollment, as generally agreed upon metrics for clinically important differences in diversity are not known. Dropout of subjects as well as limitations in recovery of sufficient DNA from low biomass samples led to lower numbers of usable quality samples than the total number that could have been obtained. Inclusion criteria were designed to capture subjects likely to complete the study protocol and who might benefit from use of the products. However, it is possible disease state was already “optimized” making benefit limited. Although our primary endpoint was to detect changes in the sinonasal microbiome rather than clinical benefit, future studies may select individuals with higher SNOT-22 scores. The variability in microbiome status of patients' sinuses also makes detecting changes more difficult. Lastly, even when community composition does not change, bacterial function may alter in response to an environmental challenge. Nonetheless, our study had high compliance with use of the rinse products and demonstrated no significant change in important clinical and microbial indices associated with use of topical xylitol or *L. lactis*.

5 | CONCLUSION

Promotion of a healthy, anti-inflammatory microbiome in patients with chronic rhinosinusitis remains an ongoing goal. Use of xylitol or *L. lactis* topically delivered via sinus rinse bottles is an option. These products are well tolerated but did not result in significantly improved

SNOT-22 scores or microbial diversity. The ability of topical products to favorably alter the microbiome remains investigational. More studies are needed to clarify the probiotic potential of these products in chronic rhinosinusitis.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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