Review

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Update on the Role of the Microbiome in Chronic Rhinosinusitis

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Abstract

Purpose of Review Chronic rhinosinusitis (CRS) is a common yet complex and heterogeneous inflammatory condition of the paranasal sinuses that is likely caused by a combination of infectious and inflammatory factors. The role of the microbiome in the pathogenesis of CRS remains poorly defined. The purpose of this review is to examine the role of the microbiome in CRS and evaluate current and emerging therapies that may alter the sinonasal microbiome.

Recent Findings There are complex interactions among the various microorganisms that make up the sinonasal microbiome with a growing body of evidence that increased microbial biodiversity may be protective against the development of CRS and patients with improved biodiversity may have better treatment outcomes. Topical and systemic antimicrobials, intranasal corticosteroids, and surgery have demonstrated transient changes to the microbiome without significant change in symptoms. The use of probiotics and bacteriophages remain areas of active investigation regarding alterations to the sinonasal microbiome.

Summary CRS seems to be associated with decreased sinonasal microbial diversity, but whether this is the cause of CRS or a downstream effect remains unclear. Additional evaluation into the role of the microbiome on CRS and the impact of therapies that may yet alter the microbiome are necessary.

Introduction

Chronic rhinosinusitis (CRS) is defined as inflammation of the paranasal sinuses that persists for greater than 12 weeks with or without acute exacerbations [1]. CRS impacts approximately 14–30 million United States adults per year, accounting for up to 8.6 billion dollars in direct annual expenditures and over 13 million office visits per year [2, 3]. Despite the prevalence of CRS, the exact etiology remains unclear, although a multifactorial mechanism is considered likely. Current literature indicates that CRS is related to multiple complexes, highly variable host-environmental interactions, for which the end result is one of a number of inflammatory endotypes that subsequently cause symptoms of CRS [4••]. Bacteria, fungi, and even viruses have long been considered among the primary causative factors of CRS [5, 6], and there has been increasing research examining the role of the sinonasal microbiome in chronic rhinosinusitis.

The microbiome consists of the collective genomes of the microorganisms living on and within the human body and has been established to play a key role in health and immune function [7]. At any one time, it is estimated that an individual may host up to 100 trillion microorganisms [8] that typically serve a mutualistic purpose to the human body. Hosts receive the benefits of improved immunologic development and metabolic function while commensal organisms gain

a nourishing environment in which to thrive [9, 10]. Greater mucosal biodiversity may play a role in limiting inflammation and protecting against infection [9], and disruptions of this previously beneficial symbiosis can transform into a destructive process and contribute to disease states such as chronic rhinosinusitis [11].

While the exact role of the microbiota in the pathogenesis of CRS remains poorly understood, recent evidence has noted an association between mucosal inflammation and decreased diversity of local bacterial communities in the paranasal sinuses [12–14]. In cases of CRS, it remains unclear whether a dysbiosis of the sinonasal microbiome is the initial cause of chronic immune response and inflammation, or if there is an inflammatory process or deficiency of immune function that alters the conditions of the sinonasal mucosa such that secondary bacterial overgrowth is allowed. The purpose of this review is to examine the existing literature regarding the role of the microbiome in CRS to include the normal and abnormal microbiome, factors that may alter this microbiome, and review the impact of current treatments options on the sinonasal microbiome. For this review, we utilized various search terms through PubMed and Google Scholar as well as forward and backwards search of citations to identify pertinent literature pertaining to the sinonasal microbiome.

The Sinonasal Microbiome

Evaluating the Sinonasal Microbiome

There has been substantial evolution in detection techniques for the sinonasal microbiome over the last few decades. Initial studies via Lefort 1 osteotomies in non-infected sinuses of patients undergoing orthognathic surgery [15] and early middle meatal cultures of healthy patients [16] led many to conclude the healthy sinuses were largely sterile. Subsequent studies using culture-based techniques were successful in identifying a number of microorganisms that were bacterial colonizers, such as coagulase-negative staphylococci [17] that were subsequently proposed to be potential pathogens that mediated infectious processes in CRS. However, these culture-dependent methods had significant limitations. Culture-dependent analysis relies predominantly on direct growth and identification of bacteria from the sample. This made cultures good for identifying the most prominent bacterial colonizers, but

selected against identifying those species that were unable to grow outside their natural microhabitat or grew in rates low enough to avoid detection by culture-based techniques [18, 19]. Currently, it is estimated that over 70% of the human microbiota is unculturable via culture-based techniques [18] and that sinus cultures are poorly representative of the sinonasal microbiota [20].

These limitations led to the advent of culture-independent techniques to further characterize the sinonasal microbiome. The Human Microbiome Project [21] was a National Institutes of Health funded project that identified and amplified the 16 s RNA gene within the desired sample, a gene that is preserved within the bacterial genome and subsequently used to quantify human bacterial diversity. The Human Microbiome Project examined the anterior nares of 242 healthy participants via 16S rRNA gene profiling and demonstrated high abundances of *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Propionibacterium*, *Corynebacterium*, and *Moraxella* [22]. It is important to note that classically, sample sites have been considered to be significant confounding factors in the evaluation of many previous studies evaluating the microbiology of the sinuses in inflammatory states. De Boeck et al. evaluated the anterior nares, nasopharynx, and maxillary/ethmoid sinuses of 190 CRS patients and the anterior nares and nasopharynx of 100 control patients. They demonstrated strong continuity for the microbiome among the different upper respiratory tract niches in CRS patients with the anterior nares most closely representing the microbiome of the sinuses [23]. Additional studies by Lal et al. and Ramakrishnan et al. demonstrated some degree of microbiome composition across sinuses in a single patient, but that the intersubject variability outweighed any intrapersonal variability and that the middle meatus is a fair representation of the microbiome of the underling sinuses [24, 25].

In summary, evaluation of the sinonasal microbiome is currently best achieved by evaluating bacterial 16 s rRNA sequencing of samples obtained from the middle meatus in the non-operated patient, and from the location of interest in the post-operative patient given inter-sinus variability.

The Role of Fungi and Viruses in the Sinonasal Microbiome

Fungi and viruses are known components of the human microbiome, but their role is uncertain, particularly in the healthy population. They will be covered here briefly but will not be fully examined as there is very limited available literature or understanding of their exact contributions. Viruses are believed to be the most abundant and diverse biological entities, consisting of 10^{13} viral particles per human individual [26]. The respiratory tract of healthy individuals has been shown to contain common viruses such as *rhinovirus*, *anellovirus*, and *enterovirus* [27]. Symptomatic viral infections can alter the microbiome [28] and bacteriophages have demonstrated the ability to alter the nasal bacterial microbiome [29]. Evaluations of the fungal microbiome have additionally been limited. *Malassezia* is the predominant fungus noted within the anterior nares and sinonasal cavity, present in 53.9% of samples, followed by *Cladosporium* (6.0%), and *Pleosporles* (2.2%) [30]. The impact of these fungal organisms in the overall microbiome remains largely unknown. *Malassezia* prevalence has demonstrated an inverse relationship

with *Propionibacterium acnes*, indicating a potential competitive inhibition of these microbes [30]. The Human Microbiome Project Consortium has also hypothesized that fungi may act synergistically with bacteria [21] and may be a contributing factor in the pathogenesis of CRS, particularly the interaction between *Candida albicans* and pseudomonas [31] and other bacteria [32, 33].

The Sinonasal Microbiome—Health Versus CRS

In 2020, the International Sinonasal Microbiome Study, the largest examination of the sinonasal microbiome to date, was published. Paramasivan et al. examined middle meatal cultures via 16S rRNA sequencing for 410 patients across 13 institutions and nine countries to establish the core microbiome in healthy and CRS patients. They found that the microbiome was highly variable amongst individuals and varied based on country, but contained a common core microbiome of *Corynebacterium*, *Staphylococcus*, *Streptococcus*, *Haemophilus, and Moraxella* in both CRS and healthy patients. In patients with CRS, there was a significant reduction in the relative abundance of *Corynebacterium* (40.3% CRS vs. 50.4% healthy) while there was a non-significant increase in *Streptococcus* in the CRS population. The remainder of the other core bacteria appeared to remain constant between healthy and CRS populations [34]. Lal et al. compared the microbiome of the middle meatus and inferior meatus in CRS patients. They found that samples in CRS patients without polyps had increased prevalences of *Streptococcus*, *Haemophilus*, and *Fusobacterium* with loss of bacterial diversity [24]. Multiple studies have noted that patients with chronic rhinosinusitis have demonstrated not only decreased bacterial diversity, but increased bacterial load and less stable bacterial networks, indicating the importance of maintaining the delicate balance between the various microorganisms maintaining the sinonasal environment [12–14].

Most microbes associated with the human-host interaction in the upper respiratory tract appear to act in a syntropic fashion with the possibility for competitive interactions between commensal organisms [35]. For instance, *Corynebacterium* species have notable inhibitory effects on the growth of *S. aureus* through attenuation of virulence by downregulation of components involved in colonization and competition for methionine and iron which hinders *S. aureus* growth [36]. In contrast, *Cutibacterium*, through production of coproporphyrin III, has been shown to induce *S.* aureus aggregation and biofilm formation in culture, which may promote dysbiosis in patients [37]. Recall that *Corynebacterium* species are the most prevalent organisms in the paranasal sinuses and that patients with CRS have significantly decreased relative abundances of *Corynebacterium* compared to healthy controls. This may indicate a potential etiology, or downstream effect, of the dysbiosis contributing to disease. Additional studies have shown that *Propionobacterium acnes* may be a key bacterial species in healthy sinus mucosa that is preventative of sinus disease. *Propionobacterium* is commonly identified in healthy mucosa and produces bacteriocin, an antimicrobial and antifungal compound that modulates immune response and its loss or removal may allow *S. aureus* and *Streptococcus* to flourish [38, 39]. Each of these interactions provide insights

into the delicate balance of the sinonasal microbiome and may indicate potential therapeutic interventions and avenues of treatment to modulate CRS.

Treatment

Systemic Antimicrobials

Systemic antimicrobials are exceedingly common in the treatment of chronic rhinosinusitis and the impact of these treatments on the sinonasal microbiome remains unclear. The European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS 2020) summarizes the current evidence regarding the use of long-term and shot-term antibiotics in the management of CRS and exacerbations of CRS. They evaluated two small placebo-controlled studies [40, 41] in CRS that demonstrated no significant effect on symptoms or outcomes in these patient populations. Long-term antimicrobial management evidence is similarly low quality with the added risk of cardiovascular events for some macrolide antibiotics [4••].

The impact of systemic antimicrobials on the sinonasal microbiome is similarly unclear. Feazel et al. cross-sectionally examined 21 patients undergoing ESS and found that antibiotic use was associated with a decreased microbial diversity and increased *S. aureus* abundance [42] In contrast, Lux et al. retrospectively examined 156 CRS patients and 90 control patients having received antibiotics within the previous year and found that CRS outcomes were similar among those who had received antibiotics and not received antibiotics, but the effect of antibiotics on the sinus bacterial community were overall minimal and unpredictable [43•]. Cherian et al. reached similar conclusions in a double-blinded placebo-controlled trial examining the effect of oral doxycycline on sinus symptoms and the microbiome. They found that there was a non-significant increase in the relative abundance of *Corynobacterium* that did not impact overall bacterial diversity or patient symptoms [44••]. In summary, there is limited evidence that systemic antibiotic use has a meaningful impact on CRS symptoms or the sinonasal microbiome, and further prospective investigations are required. The findings of these studies are summarized in Table 1.

Topical Antimicrobials

Topical antimicrobials have been used in the management of CRS to attempt to address the potential role of biofilm from either *S. aureus* or *Pseudomonas aeruginosa* [45], although more recent studies have indicated other microorganisms may be involved [46]. EPOS 2020 [4••] examined seven randomized-controlled trials evaluating the role of topical antimicrobial therapy in CRS and found that four studies did not show significant improvement of symptoms over treatment without antibiotics [47–50]. One study with culture-confirmed staph in post-surgical patients found that high-volume irrigations

Table 1. Summary of studies examining the impact of systemic antimicrobials on the sinonasal microbiome

Study	Year	Number of patients	Study design	Summary of findings
Lux, et al	2020	156 patients with CRS, 90 control patients	Retrospective Review	Clinical outcomes were similar among CRS patients receiving and not receiving antibiotics. The effect of antibiotics on the sinonasal microbiome were minimal and unpredictable
Cherian, et al	2020	50 patients total with matched controls: 16 in oral doxycycline group	Double-blinded, randomized placebo-controlled trial	Clinical improvement was significant with oral and topical steroids, but not empirical antibiotics. There were some microbiome changes with various treatments, but these were inconsistent and without clear clinical significance
Feazel, et al	2012	15 patients with CRS, 5 control patients	Cross-sectional Observational study	Patients with CRS undergoing antimicrobial treatment demonstrated decreased microbial diversity and increased abundance of *Staphylococcus aureus*

with mupirocin seemed to eradicate *S. aureus* better than oral antibiotics; although, lack of control group in that study and methodological concerns limited any further conclusions [51]. The impact of topical antimicrobials on the microbiome is uncertain. No studies directly examined the impact of topical antimicrobial therapy on the microbiome.

Intranasal Corticosteroids

Topical intranasal corticosteroids (INCS) are the mainstay of treatment in chronic rhinosinusitis and recommended for symptom relief [1, 4••]. There has been limited evaluation into the impact that INCS have on the microbiome. Cherian et al. in their RCT examining doxycycline also examined patient populations with oral prednisolone and topical budesonide, each with a placebo. They found that there was a significant increase in bacterial diversity in the topical budesonide group that returned to baseline composition within 3 weeks of cessation of therapy [44••]. Based on this study, it is unclear what the long-term implications of continued INCS therapy would have been on the sinonasal microbiome. Similarly, Ramakrishnan et al. examined the sinonasal microbiome of four patients treated with topical mometasone serially over a period of 8 weeks and found transient changes in the relative abundance of multiple microbes to include *Staphylococcus* and *propionibacteria* during treatment that persisted at least 2 weeks after cessation [52]. Latek et al. similarly examined the sinonasal microbiome and quality-of-life changes in pediatric patients randomized to treatment with either topical mometasone or topical saline for 12 weeks. They noted increased nasopharyngeal microbiome richness that was associated with clinical improvement after completion of therapy [53]. This study did not follow patients after completion of therapy to determine if these changes to the microbiome were transient in nature.

Surgery

Endoscopic sinus surgery (ESS) is the mainstay of treatment for the management of CRS recalcitrant to medical therapies [4••]; however, the impact of surgery on the sinonasal microbiome and the impact of the sinonasal microbiome on surgical outcomes remains reliant on small studies. Cleland et al. examined the microbiome in 23 patients with CRS and 11 controls undergoing pituitary surgery and found that microbiome diversity decreased more significantly in the CRS group after surgery. They also found that patients with better post-operative symptom control following surgery had higher levels of *Acinetobacter johnsonii* and lower levels of *S. aureus* [54]. In contrast, Jain et al. examined the microbiome of 23 patients undergoing ESS via middle meatal swabs at multiple time points after surgery and noted that ESS was associated with increased bacterial richness with substantial intersubject variability [55].

Only a few studies have examined the role of the sinonasal microbiome on post-operative outcomes. Ramakrishnan et al. found increased relative abundances of *Corynebacterium* before surgery was associated with improved post-operative outcomes [56]. This may be indicative of the importance of

the inhibitory effects of *Corynebacterium* on the growth of *S. aureus* discussed previously. The presence of *S. aureus* has been associated with poorer post-operative outcomes, principally through the formation of biofilms [57, 58] and intracellular colonies of *S. aureus* [59]. Gan et al. similarly examined the impact of the microbiome on surgical outcomes in 77 patients with CRS and nasal polyps, finding that increased relative abundances of *Corynebacterium* and *Dolosigranulum* were inversely associated with *S. aureus* and associated with improved sinonasal outcomes after surgery [60]. Table 2 summarizes the studies examining the impact of surgery on the microbiome and the influence of microbiome factors on surgical outcomes.

Probiotics

Probiotics are living microorganisms that, when administered in adequate amounts, are thought to confer health benefits to the host. These have been well-investigated in gastrointestinal research, but the literature remains limited when discussing the sinonasal microbiome and chronic rhinosinusitis. A common trend among the existing literature regarding the sinonasal microbiome seems to be that patients with CRS demonstrate a relative lack of sinonasal biodiversity, overgrowth of pathogenic bacteria such as *S. aureus*, and relative decrease in abundance of potentially protective organisms such as *Corynebacterium* spp. It follows that a means to increase the relative abundance of *Corynebacterium* spp and/or means to reduce the relative abundance of *S. aureus* may improve symptoms relating to CRS.

Multiple studies have evaluated this association. In 2000, Uehara et al. artificially implanted a strain of *Corynebacterium* into the nares of 17 asymptomatic *S. aureus* carriers and demonstrated complete eradication of *S. aureus* in 71% of participants [61]. Menberu et al. took this a step further and evaluated the impact of *Corynebacterium accolens* on *S. aureus* biofilm growth and methicillin-resistant *S. aureus* (MRSA) isolates from CRS patients. They found that *C. accolens* supernatant induced a significant reduction in metabolic activity and biofilm formation of *S. aureus* and MRSA [62•]. Murine studies have demonstrated that probiotic use may have a role in mediating the sinonasal inflammation associated with CRS. Abreu et al. showed that instillation of *Lactobacillus sakei* and *Corynebacterium tuberculostearicum* could abrogate goblet cell hyperplasia and mucin hypersecretion by pathologic species in a depleted native microbiota, indicating a protective effect of *L. sakei* on the sinus epithelium that was induced with replacement via probiotic irrigation [63]. Cleland et al. similarly examined a murine model of sinusitis and found that instillation of *S. epidermidis* was able to convey a protective effect against the activity of *S. aureus* in sinusitis [64].

Human studies regarding the impact of probiotics on the sinonasal microbiome are limited and highly variable in outcomes and bacteria examined. Only a few studies have evaluated the use of oral probiotics on the sinonasal microbiome. Gluck and Gebbers evaluated 209 volunteers who consumed a fermented milk drink containing *Lactobacillus*, *Bifidobacterium*, and *Streptococcus* or standard yogurt for 3 weeks and found a substantial reduction in relative concentrations of *S. aureus*, *S. pneumoniae*, and *Haemophilus infuenzae*

Table 2. Summary of studies examining the impact of surgery on the sinonasal microbiome and microbiome impacts on outcomes

Study	Year	Number of patients	Study design	Summary of findings
Studies examining surgical impact on sinonasal microbiome				
Jain, et al	2017	23 patients with CRS	Prospective cohort	Unpredictable shifts in bacterial community composition were seen post-operatively. Sinus surgery was associated with increased bacterial richness and changes in bacterial communities were driven by intersubject variability more than other factors
Cleland, et al	2016	23 patients with CRS, 11 controls	Prospective cohort	Sinonasal microbial diversity declined in the CRS group after surgery. Increased mean relative abundances of *Acinetobacter johnsii* was associated with improved quality of life after surgery
Ramakrishnan, et al	2015	56 patients with CRS, 26 controls	Cross-sectional	Bacterial biodiversity was similar between the CRS and control groups. Purulence and comorbid asthma were associated with significant alterations in the microbial community composition. Those patients with CRS with better outcomes had higher relative abundances of *Actinobacteria*
Studies examining impact of microbial factors on surgical outcomes				
Gan, et al	2021	77 patients with CRSwNP	Prospective cohort	Recurrence of nasal polyps after endoscopic sinus surgery may be associated with reduced abundance of protective microorganisms (*Corynebacterium* and *Dolosigranulum*) and increased abundance of pathogenic organisms (S. aureus)
Ou, et al	2016	25 patients with CRSwNP, 15 patients with CRSsNP, 8 controls	Prospective cohort	Intracellular Staphylococcus aureus was more prevalent in CRSsNP than CRSwNP and was associated with increased lymphocytic and total inflammatory cells without an increase in symptoms
Singhal, et al	2010	51 patients with CRS	Prospective, blinded cohort	Biofilms were found in 71% of CRS patients. Patients with biofilms had worse pre-operative radiology and nasal endoscopy scores
Psaltis, et al	2008	40 patients with CRS	Retrospective cohort	Bacterial biofilms were noted in half of patients with CRS. Those with biofilms had worse post-operative outcomes based on radiologic, endoscopy, and outcome measures

in healthy populations [65]. Mukerji et al. took this a step further and evaluated the use of effect of oral *Lactobacillus rhamnosus* vs. placebo for 4 weeks on 77 patients with CRS. They found that there was a transient improvement in baseline SNOT-20 scores at 4 weeks in the probiotic group that returned to baseline by 8 weeks without any changes in symptom frequency [66]. Two studies have evaluated the use of oral *Enterococcus faecalis* on CRS. Habermann et al. in a double-blinded placebo-controlled study found that a 6-month course of *Enterococcus faecalis* reduced the frequency of CRS exacerbations that was sustained for 8 months post-therapy cessation [67]. Similarly, Kitz et al. treated patients with 8 weeks of *Enterococcus faecalis* and found a reduction in frequency and severity of sinusitis exacerbations in children [68].

A number of studies have examined the role of topical probiotic applications in the treatment of CRS. Martensson et al. applied topical honeybee lactic acid via a nasal spray device to 20 patients with CRS for a 2-week period and found no changes in symptom scores, inflammatory markers, or sinonasal microbiome [69]. Two studies have evaluated the role of *Lactobacterium lactis* W136 in topical sinonasal irrigations. Endam et al. performed the first prospective trial on 24 patients with refractory CRS for 14 days and found that probiotic irrigations were safe and showed improvement in sinonasal symptoms without significant changes in the sinonasal microbiome aside from an increase in the bacteria *Dolosigranulum pigrum* [70]. Lambert et al. enrolled 25 subjects with CRS and 10 control patients and treated with either *L. lactis* W136 or xylitol in a non-blinded fashion and found no significant changes in SNOT-22 scores following treatment [71•]. Despite the lack of evidence supporting their use, there are commercial formulations of probiotic irrigation currently on the commercial market. Cho et al. examined one of these commercially available *L. lactis* W136 formulations and found that, when grown in an anaerobic chamber, *L. lactis* induced the growth of a mucoid strain of *P. aeruginosa* in an in vitro co-culture, raising the potential concern that these formulations may contribute to the growth of pathologic bacterial strains and that more research is necessary [72•]. Table 3 details the studies examining the use of probiotics in human subjects.

Bacteriophages

Bacteriophages are viruses that infect and replicate only in bacterial cells. They are species-specific and generally target a single bacteria or class of bacteria [73]. As such, there has been a recent interest in the use of bacteriophages to alter the sinonasal microbiome and/or disrupt the presence of biofilms in the management of CRS. A recent review article examining the role of bacteriophages in multiple indications, to include CRS, notes that while the literature is expanding regarding the use of bacteriophages and phage therapy appears safe based on multiple randomized-controlled trials, there has been limited data investigating in vivo efficacy, barriers to understanding of phage pharmacology/application that have limited clinical applicability of these novel therapeutics to date [74].

Only a handful of studies have looked specifically at the role of bacteriophages in CRS patients. Dobretsov et al. performed a randomized,

Table 3. Summary of human studies examining the impact of probiotics on the sinonasal microbiome

Study	Year	Number of patients	Study design	Probiotic administration	Summary of findings
Oral probiotic administration					
Mukerji, et al	2008	77 patients with CRS	Double-blinded, randomized placebo-controlled trial	Treatment with oral *Lactobacillus rhamonsus* or placebo	The probiotic group demonstrated a significant reduction in baseline SNOT-20 scores at four weeks that returned to baseline by eight weeks without change in symptom frequency or medication use
Glück, et al	2003	209 healthy volunteers	Open prospective trial	Oral consumption *Lactobacillus spp, bifidobacterium, and streptococcus* or standard yogurt	There was a significant reduction in nasal potentially pathogenic bacteria to include a reduction in relative concentrations of S. aureus, S. pneumoniae, and *Haemophilus infuenzae*
Habermann, et al	2002	157 patients with CRS	Double-blinded, randomized placebo-controlled trial	Treatment with bacterial oral immunostimulant of autolysate of *Enterococcus faecalis*	The experimental group experienced a 56% reduction in the rate of sinus infections compared to placebo that was sustained for 8 months after cessation of therapy
Kitz, et al	2013	204 children with recurrent rhinosinusitis	Randomized prospective trial	Treatment with oral *Enterococcus faecalis* autolysate after acute exacerbation	The number of sinusitis episodes, duration of sinus symptoms, and duration of subsequent sinusitis episodes was lower in the probiotic group when compared to controls
Topical nasal probiotic administration					
Lambert, et al	2021	25 patients with CRS and 10 controls	Non-blinded prospective crossover trial	Nasal irrigations with *Lactobacillus lactis W136* or xylitol	There were no major clinical or microbiome-level effects due to treatment with topical irrigation products

Table 3. (continued)

Study	Year	Number of patients	Study design	Probiotic administration	Summary of findings
Endam, et al	2020	24 patients with CRS	Prospective, open-label trial	Nasal irrigations of *Lactobacillus lactis W136*	Treatment was associated with an improvement in sinus symptoms, quality of life, and mucosal scores that was persistent in the 14-day observation period. There was an increase in prevalence of *Dolosigranulum pigrum*, a potentially protective bacterial species
Mårtensson, et al	2017	20 patients with CRSsNP	Double-blinded, randomized, crossover, sham-controlled trial	Nasal administration of honeybee lactic acid bacteria	There was no change in symptom scores, microbiological composition, nor levels of inflammatory products between study groups

double-blinded, placebo-controlled study examining the impact of an intranasal gel with a bacteriophage mixture in patients undergoing endoscopic sinus surgery for CRSwNP. Patients were provided an intranasal bacteriophage gel with activity against 32 types of bacteria to include *S. aureus*, *Pseudomonas aeruginosa*, *E. coli*, and multiple others twice a day for 10 weeks compared to placebo. Patients receiving the bacteriophage gel were noted to have a decrease in total sinonasal microorganisms, *Enterobacteriaciae*, *S. aureus*, and complete absence of *Streptococci* when compared to placebo at 30 days [75]. The authors did not comment on if these changes in the microbiome correlated with any changes in clinical outcomes for patients.

Drilling et al. have examined the possibility of using bacteriophages specific to *S. aureus* to specifically target biofilm formation. They found that in an in-vitro model that bacteriophages are effective anti-biofilm agents [76] and that in a sheep model can be safely applied via suspension in sinus irrigations for a period of 20 days without inflammatory infiltration or sinus mucosal damage [77]. More recently, Ooi et al. conducted a phase 1 clinical trial of nine participants with treatment recalcitrant CRS with positive *S. aureus* cultures and found that irrigations with bacteriophage were generally well tolerated with eradiation of infection in 2/9 patients [78]. Since that time, there have been additional case reports, such as that published by Rodriquez et al. examining the case of a refractory MRSA-related CRS patient successfully treated with combination of oral antibiotics and systemic and intranasal phage therapy with eradication of infection/biofilm [79].

Conclusion

Our understanding of the role of the microbiome in chronic rhinosinusitis is continually evolving. Current evidence indicates that the sinonasal microbiome is composed of complex and highly variable bacteria, fungi, and viruses that exist in a commensal balance. Disruptions to this balance may encourage the growth of pathogenic strains of bacteria, and thus contribute to symptoms associated with CRS. It remains unclear though whether this disruption in the microbiome is a causative factor in the pathogenesis of CRS or if changes to the microbiome are a downstream effect. Larger prospective studies would be necessary to further elucidate this relationship. Treatments for CRS have variable effects on the sinonasal microbiome and studies attempting to manipulate the microbiome remain limited. Treatment of the sinonasal microbiome is an ever-evolving area of research that requires larger prospective studies to guide further therapeutic possibilities.

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Author Contributions

JLF: concept and design, final approval and supervision of project, acquisition of data, drafting and critical revision of manuscript, preparation of figures and tables. JTL: concept and design, final approval and supervision of project, acquisition of data, drafting and critical revision of manuscript, preparation of figures and tables.

Declarations

Competing Interests
The authors declare no competing interests.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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