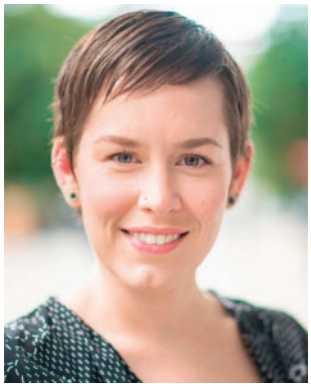
Chronic rhinosinusitis: a microbiome in dysbiosis and the search for alternative treatment options



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Chronic rhinosinusitis (CRS) is a common chronic disease. While CRS is a multifactorial disease, many cases involve an imbalance in the sinus bacterial microbiome. This article reviews the composition of the healthy human sinus microbiome compared to the microbiome of CRS patients. Issues with current treatment options, particularly antibiotics, are discussed. Insights into the future of CRS treatment are also explored, principally with regards to probiotics.

Rhinosinusitis is a condition characterised by paranasal sinus and nasal inflammation. Symptoms include nasal blockage/obstruction/congestion, facial pain/pressure, reduction or loss of smell, and rhinorrhoea; when these continue for over 12 weeks, the condition is classified as chronic rhinosinusitis (CRS)[1]. CRS is one of the most prevalent chronic diseases worldwide, conservatively affecting 5–6% of US adults[2] and 8.5% of Australian adults[3]. The economic burden of CRS in the US alone is approximately US$22 billion annually[4].

Like many chronic diseases, CRS has a complex etiology, with interplay between microorganisms (bacteria, fungi and viruses), environmental disturbances (e.g. pollutants or smoking) and host factors (e.g. the immune system and underlying diseases)[5]. This article explores the role that bacteria play in CRS by examining recent research suggesting that disturbances to the sinus microbiome are involved in CRS pathophysiology.

CRS and the sinus microbiome

A microbiome is a collective term for all of the microorganisms present in an environment. Various groups of microorganisms can cause disturbances to the sinus microbiome, which can sometimes contribute to the development of CRS. For instance, an acute viral infection is the cause for many cases of sinus microbiome disturbance, but this is a short-term disturbance[1,6]. Also, while fungi are not considered primary etiologic agents of CRS, allergies to some fungi can result in a distinct condition with similar symptoms as CRS called Allergic Fungal Rhinosinusitis[5]. However, the group of microorganisms that are the biggest players in CRS are bacteria[1,5].

In the past, healthy sinuses were considered sterile environments, and CRS developed when bacteria colonised these sinuses[7]. Nowadays, it is recognised that healthy sinuses house diverse microbiomes with both commensal bacteria and potentially pathogenic bacteria; the pathogens present in these healthy sinuses are present at levels too low to cause disease[6,7]. The commensal microbes form a symbiotic relationship with the host, such as by forming a barrier against incoming external pathogens[8]. An imbalance of the sinus microbiome – termed microbiome dysbiosis – is seen in many cases of CRS, as seen by an overabundance of opportunistic pathogens and loss of key commensals[5,6,8,9]. The immune system is then activated due to pathogen invasion through epithelial tight

junctions and release of various immunostimulatory molecules, thus resulting in inflammation[1,5] (Figure 1).

Determining differences in the bacterial makeup of CRS or non-CRS sinuses is a relatively novel area of research. This is due to both the recent change in our understanding of CRS pathophysiology and recent advances in microbiome characterisation methods. Traditional culture-dependent methods fail to truly represent the sinus microbiome[9,15], so truly accurate insights into CRS versus healthy microbiomes are from a currently limited number of molecular-based studies[9–12,15–18].

Further adding to the complexity of CRS is that there does not seem to be a 'model' CRS microbiome; that is, each CRS patient has a unique sinus microbiome composition[15,16]. Also, even within a single CRS patient, the microbiome of each sinus is different[19]. However, after taking these sources of variation into consideration, there are still certain features that can distinguish between CRS and non-CRS microbiomes, as described in the next two sections.

Balance of bacterial taxa

Compared to healthy sinuses, CRS sinuses have decreased bacterial diversity (the total number of bacterial taxa) and evenness (the relative proportion of each taxon)[8,10–12]; in other words, healthy sinuses have many different types of bacteria present in similar numbers, while CRS sinuses have few types of bacteria present, and of those some are overabundant while others are barely present (Figure 1). In ecology terms, these decreases are mainly due to selective enrichment of certain 'disease-producing' species and depletion of other 'protective' species.

Mostly commensal taxa are depleted in CRS patients; notably, decreases in *Bacteroidetes* spp., *Prevotella* spp.[11], *Lactobacillus* spp.[10], *Peptoniphilus* spp., *Propionibacterium acnes*[9], *Acinetobacter johnsonii* and *Corynebacterium confusum*[18] have been observed.

Other bacterial taxa are found to be enriched in CRS microbiomes. Increases in *Pseudomonas* spp.[16], *Corynebacterium* spp.[10,16], certain *Streptococcus* spp., *Staphylococcus aureus*, *Propionibacterium acnes* and *Haemophilus influenzae*[15,16] have been reported in CRS. Abreu *et al.*[10] notably found enrichment of a novel sinopathogen *Corynebacterium tuberculostearicum*, typically a commensal when present on skin. Of particular importance to CRS is *S. aureus*. Most microbiome studies found that *S. aureus* was enriched in CRS patients; some even found it to be the most abundant organism in CRS sinuses[9,11,12,16,18]. Here it is important

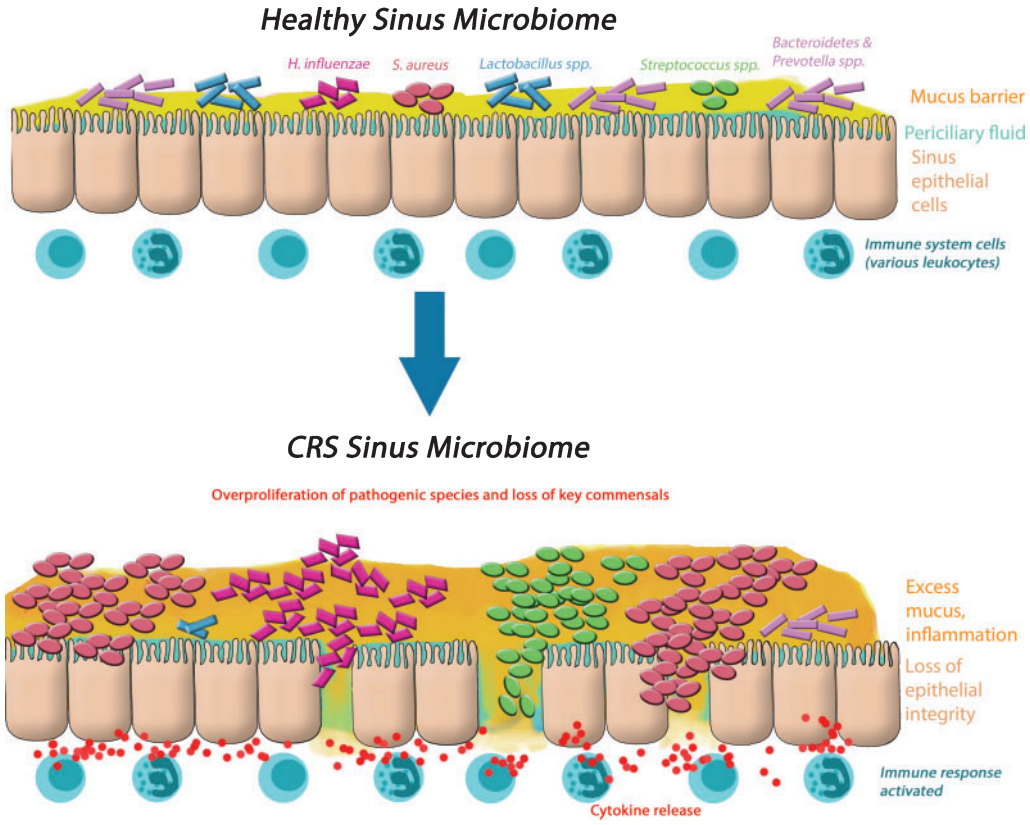

Figure 1. Nasal mucosa microbiomes of healthy versus CRS patients. The normal nasal mucosa is colonised by a highly diverse dynamic mix of commensal microbes, and some pathogenic microbes at low abundances. Perturbations to the microbiome can lead to microbiome dysbiosis; now the sinuses have low species diversity and evenness, with loss of critical commensal species and selected enrichment of pathogens. This then leads to a loss of epithelial integrity, immune activation and sinus inflammation. The bacterial taxa presented here are a few of the commensal and pathogenic species that have been implicated in CRS disease progression. This figure is adapted from the information in the following references[5,6,8–16].

to emphasise the problem of 'correlation vs causation', as seeing increases of certain taxa in a disease state is insufficient evidence to conclude that those taxa are causing the disease. With particular regard to *S. aureus*, no study has been carried out to explicitly determine whether or not an increased sinus level of *S. aureus* will cause CRS. However, current research on *S. aureus* in CRS[12,18,20,21] indicates that *S. aureus* increases the severity of CRS, and is at the very least involved in CRS development.

Bacterial load

Bacterial load is the total number of bacteria in a microbiome[8]. There is currently disagreement in the literature on the correlation between CRS and bacterial load. Boase *et al.*[9] and Choi *et al.*[11] found an increased bacterial load in CRS patients and suggested that a rise in bacteria, possibly from external sources, causes CRS. However, Abreu *et al.*,[10], Feazel *et al.*[12] and Ramakrishnan *et al.*[13] found no difference in burden between the two groups. Feazel *et al.*[12] pointed out that pathogens are present in low abundances in healthy patients, and are selectively enriched in CRS patients, and suggested that shifts in the existing bacterial community, rather than influxes of external pathogenic bacteria, cause CRS[12]. While this hypothesis is currently favoured[5,8], more studies are required to establish a causal link.

Current CRS treatment

If a patient presents to a clinic with over twelve weeks of the rhinosinusitis symptoms as mentioned previously, a preliminary test is to check for any allergy. If positive for allergy, the condition is termed allergic rhinosinusitis[1], which is out of the scope of this article. On the other hand, if the rhinosinusitis is not caused by allergy, it is diagnosed as CRS and treated accordingly. Treatment options are initially saline nasal irrigation, antibiotics, followed by topical or oral corticosteroids[1]; if these treatments fail to improve symptoms, sinus surgery may be necessary[1]. Despite their only partial success rate, antibiotics are the current most widely used treatment option for CRS (50–70% of CRS diagnoses result in the prescription of an antibiotic) due to their ease of access, low costs and low complexity of intervention[22,23]. However, using antibiotics to treat CRS seems to be a short-term solution with long-term problems. Managing a chronic condition with ongoing antibiotic administration creates conditions particularly favourable for the rise of antibiotic resistant bacteria[23,24]. Penicillin-resistant pathogens have been found in extensively antibiotic-treated CRS patients since the 1980s[25]. Furthermore, Bhattacharyya and Kepnes[24] found that extensively treated sinus microbiomes have increased abundances of methicillin-resistant *S. aureus* (MRSA). They found that 3.6% of all bacterial isolates from CRS sinuses were MRSA, which is much higher than the general population[24]. Bhattacharyya and Kepnes[24] also found that resistance rates against erythromycin, another key antibiotic, increased in CRS microbiota from 30% to 69% over five years.

This issue of emerging resistance against the most common treatment for CRS has encouraged several researchers to investigate alternative treatment options. One approach that has been recently garnering interest is the use of probiotics to restore a healthy microbiome in CRS patients.

Probiotics in CRS

A probiotic is defined as '...a live microorganism that, when administered in adequate amounts, confers a health benefit on the host'[26]. This benefit often involves restoring a healthy commensal microbiome by competing with pathogenic taxa, either by direct attack or by better-filling a niche[6,27]. Probiotics have been used against several diseases, such as traveller's diarrhoea, otitis media, and irritable bowel syndrome, as reviewed by Goldin and Gorbach[28]. Using probiotics to treat CRS is a very novel research area. While research is limited, the studies currently available show promise for various probiotic species that can reduce colonisation of different sinus pathogens.

For instance, Cleland *et al.*[29] co-inoculated mice with *Staphylococcus epidermidis* (potential probiotic) and *S. aureus* (CRS pathogen). They found that these mice had lower goblet cell counts (a marker for airway inflammation) compared to *S. aureus* only inoculated mice, suggesting that the *S. epidermidis* interfered with the pathogenicity of *S. aureus*. Further, Abreu *et al.*[10] found that *Lactobacillus sakei* (potential probiotic) reduced the colonisation levels of *C. tuberculostearicum* (CRS pathogen) in microbiome-depleted mice sinuses, again suggesting that the probiotic had an inhibitory effect on the pathogen. Finally, Uehara *et al.*[30] repeatedly administered a commensal *Corynebacterium* species into the nares of healthy human participants who were natural nasal carriers of *S. aureus*. This treatment eradicated *S. aureus* in the nares of 13 out of 17 participants.

It is important to acknowledge that this research field is still in its infancy. Each study reviewed here only explored one probiotic and its effect on one pathogen; as CRS is a complex disease involving whole microbiome dysbiosis, more comprehensive studies looking at multiple probiotic/commensal species interactions are certainly called for. However, the results of these studies at least show enough promise to warrant future research in this area.

Conclusion

Overall, it is clear that the etiology of CRS is not as simple as infection by pathogenic bacteria. Rather, bacteria play a role in the

development of CRS through the dysbiosis of the sinus microbiome. Compared to a healthy sinus microbiome, a CRS microbiome has a decrease in bacterial diversity and evenness, with a loss of some commensal species and overabundance of some pathogenic species. With the emergence of antibiotic resistant bacteria, researchers are starting to explore other treatment options, such as probiotics. These treatments aim to restore the sinus microbiome to normal, which may contribute to improving the symptoms of CRS.

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Biographies

Professor Anders Cervin is a Professor in Otolaryngology (Rhinology) and a Senior Staff Specialist at the Department of ENT, Head and Neck Surgery, Royal Brisbane and Women's Hospital. Professor Anders Cervin's expertise includes endoscopic sinus surgery as well as endoscopic anterior skull base surgery. Research focus of our group is on the role of the microbiota in health and disease in chronic airway disease and the possibility to modify disease expression by modifying the microbiome of the nasal cavity and sinuses.

Dr Hanna Sidjabat is a Research Officer of Infection and Immunity Theme at the University of Queensland, UQ Centre for Clinical Research. Dr Sidjabat is working within Professor Anders Cervin's group, leading the microbiology work of microbiome of upper respiratory tract of chronic rhinosinusitis (CRS) study and healthy participants as well as otitis media in the Australian Indigenous population. Dr Sidjabat has been leading the *in vitro* development of probiotic strains that can be used to treat airway diseases.

Miss Amanda Bordin is an Honours student of Dr Sidjabat and Professor Cervin. Her honours project is on genomic and proteomic features of *Lactobacillus* spp. and *Staphylococcus aureus* with applications to chronic rhinosinusitis.