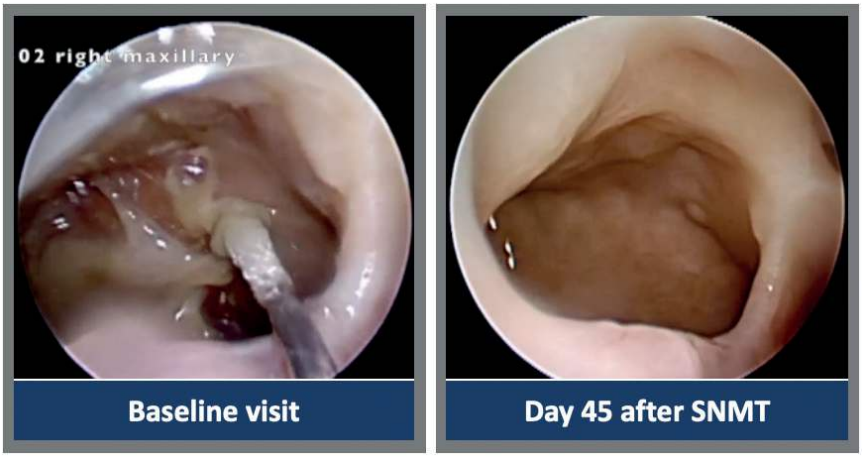
Targeting the microbiome in chronic rhinosinusitis

BY JUAN CARLOS HERNAIZ, SANDEEP K GILL, AMEE R MANGES AND AMIN R JAVER

Researchers at St Paul's Sinus Centre and UBC in Vancouver are testing a novel treatment for CRS: transferring mucus from a healthy donor into a patient's sinuses.

Chronic rhinosinusitis (CRS) is one of the most common diseases managed by otolaryngologists worldwide. Although some cases can be managed medically, most patients eventually require endoscopic sinus surgery. Surgical success rates have dramatically improved over the last 20 years. However, 15-20% of patients still suffer from recalcitrant disease and require advanced care. Treatment options include oral corticosteroids, low-dose long-term macrolides, revision surgery, or some combination of these treatments. More recently, monoclonal antibodies that target type 2 inflammation (e.g. dupilumab, mepolizumab), have revolutionised CRS care by reducing the recurrence rate for CRS patients with nasal polyps. However, they come at considerable cost to both patients and the healthcare system. More importantly, there is a subset of patients whose recurrence is likely driven by microbiological factors and who are unlikely to benefit from these therapies.

Most rhinologists will agree that this latter group represents the most challenging CRS patients to treat. Typically, they are individuals with chronically infected sinuses who suffer from ongoing purulent discharge despite maximal medical therapy. Treatment strategies vary from centre to centre but usually involve topical antimicrobials (e.g. mupirocin or betadine rinses) with or without extended sinus surgery (e.g. Draf 3 frontal sinusotomies, maxillary mega antrostomies, reboot, etc.). Unfortunately, failure is common in these cases, leaving patients and providers with few other treatment options.



It is unclear why some individuals become 'chronically infected' after surgery, but evidence suggests that the microbiota play a key role. For example, bacterial biofilm during sinus surgery is associated with worse endoscopic scores at six months [1]. Similarly, having a less diverse bacterial microbiota increases the likelihood of disease recurrence [2]. One meta-analysis showed that, compared to healthy individuals, patients with CRS tended to have fewer healthy commensals [3]. Thus, it is likely that microbial dysbiosis – the compositional and functional imbalance of a microbial community – can cause and contribute to CRS recurrence.

The exact role that dysbiosis plays in CRS is unclear. Given the long disease latency of CRS, it is difficult to discern whether the microbial dysfunction is a cause or a consequence of inflammation. For example, a cohort study that could evaluate whether decreased bacterial diversity in the sinuses leads to CRS would be extremely costly and impractical, while a case-control study that compares CRS cases to healthy controls would fail to establish temporality. In-vitro studies offer some insight into the pathophysiology of CRS but are insufficient to answer this question, leaving us in a 'chicken-and-egg' situation.

Regardless of what comes first – microbial dysbiosis or sinus inflammation – all our treatment options currently target the underlying inflammatory cascade. But what if we focused our efforts on restoring the dysbiotic microbiota instead?

Microbiota-altering treatments are safe and effective in other fields of medicine. Fecal microbiota transfers (FMT) are highly effective at eradicating *C. difficile*. from the gut, restoring the gut microbiota and resolving hospital-associated *C. difficile* diarrhoea. FMT has been shown to be beneficial in treating ulcerative colitis and can improve signs and symptoms of extra-intestinal diseases, like atopic dermatitis [4,5]. If FMT can treat both infectious and non-infectious diseases, it is reasonable to assume that a similar strategy could help manage recalcitrant CRS.

Our group recently published a pilot study investigating the safety and efficacy of a sinonasal microbiota transfer (SNMT) (https://onlinelibrary.wiley.com/doi/full/10.1002/alr.23352). In this landmark study, we randomised nine patients to one of three interventions: SNMT, antimicrobial photodynamic therapy (aPDT), or a combination of SNMT and aPDT.

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Material for SNMT was endoscopically harvested directly from the middle meatus of healthy adults, all of whom screened negative for transmissible diseases and were free of sinus disease. The transfer material was then homogenised and applied under endoscopic view directly into the affected patient’s sinuses. aPDT is a non-antibiotic treatment that combines light with a photosensitiser to create free radicals that kill microbial cells. It is performed under endsocopic vision using a fleixble balloon light catheter in under five minutes. We decided to test SNMT with and without aPDT to evaluate whether pre-treating the sinuses, to eliminate the dysbiotic microbiota, before the transfer could enhance its efficacy.

Patients randomised to the aPDT arms were treated on days zero and seven, while SNMT was done on days seven and eight, followed by a repeat infusion on days 21 and 22. All participants were closely followed and evaluated for possible adverse events throughout the trial. The primary outcome was the change from baseline in the modified Lund-Kennedy endoscopic score, and secondary outcomes included quality of life scores using the SNOT-22 questionnaire and microbial metagenomics.

Two out of three SNMT recipients improved their endoscopic and SNOT-22 scores at 30 days post intervention, and all three sustained improvements after six months of follow-up. In contrast, two out of four patients who received aPDT plus SNMT improved after 45 days but worsened during follow-up. Participants treated with aPDT alone had short-term improvement in their signs and symptoms followed by worsening and a return to baseline. These results suggest that SNMT alone can improve the endoscopic appearance of the sinonasal cavity and improve quality of life.

Regarding bacterial metagenomics, participants who received SNMT showed a transient improvement in their alpha diversity – a measure of microbiota diversity at a given time – but did not demonstrate a permanent shift toward the donor’s microbiota profile. However, their microbiota profiles did change compared to baseline. In other words, SNMT appears to transiently improve diversity and possibly ‘shift’ the sinus microbiota composition.

Based on these promising results, we are now testing SNMT in a double-blind, placebo-controlled randomised trial (Clinical Trials ID NCT05454072). As of April 2024, we have recruited 50% of the sample and are awaiting the results of the first interim analysis.

If proven successful, the SNMT trial will demonstrate that this microbiota-altering therapy can help sinus microbiota recovery, lessen inflammation, and improve CRS outcomes. Our group is also working on parallel studies focusing on the possible mechanisms behind SNMT efficacy (or lack thereof). Knowing which component of the transfer material is responsible for its potential efficacy will be key moving forward. Another critical implementation question is whether we can simplify the process and store SNMT sinus mucus material for future use.

Time will tell whether SNMT, or a version of it, will become an effective and practical therapy for CRS. However, what once sounded like an unorthodox idea is being seriously tested in a randomised trial. Regardless of the eventual outcome, we hope our research will inspire others to think outside the box and find creative solutions to a complex clinical problem in desperate need for treatment innovation.

References

1. Singhal D, Psaltis AJ, Foreman A, Wormald PJ. The impact of biofilms on outcomes after endoscopic sinus surgery. *Am J Rhinol Allergy* 2010;**24(3)**:169–74.
2. Ramakrishnan VR, Hauser LJ, Feazel LM, Ier al. Sinus microbiota varies among chronic rhinosinusitis phenotypes and predicts surgical outcome. *J Allergy Clin Immunol* 2015;**136(2)**:334–42.e1.
3. Wagner Mackenzie B, Waite DW, Hoggard M, et al. Bacterial community collapse: a meta-analysis of the sinonasal microbiota in chronic rhinosinusitis. *Environ Microbiol* 2017;**19(1)**:381–92.
4. Kim JH, Kim K, Kim W. Gut microbiota restoration through fecal microbiota transplantation: a new atopic dermatitis therapy. *Exp Mol Med* 2021;**53(5)**:907–16.
5. Porcari S, Benech N, Valles-Colomer M, et al. Key determinants of success in fecal microbiota transplantation: From microbiome to clinic. *Cell Host Microbe* 2023;**31(5)**:712– 33.

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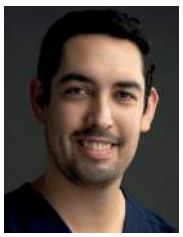

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Declaration of competing interests:
None declared.