TARGETING THE MICROBIOME IN CHRONIC RHINOSINUSITIS

Word count (1,120)

Researchers at the St. Paul's Sinus Centre and the School of Population and Public Health at the University of British Columbia are testing a novel approach to treating recalcitrant chronic rhinosinusitis: transferring mucus from a healthy donor into the patient's sinuses.

Chronic rhinosinusitis (CRS) is one of the most frequent 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 in the last 20 years. However, 15 to 20% of patients still suffer from recalcitrant disease and require advanced care[1,2]. 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 revolutionized CRS care by improving the recurrence rate for CRS patients with nasal polyps[3]. However, they come at a considerable cost to both patients and the healthcare system[4]. 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 some of 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 plays a key role. For example, bacterial biofilm during sinus surgery is associated with worse endoscopic scores at six months[5]. Similarly, having a less diverse bacterial microbiome increases the likelihood of disease recurrence[6]. One meta-analysis showed that, compared to healthy individuals, patients with CRS tended to have fewer healthy commensals[7]. 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, though. 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 evaluates whether decreased bacterial diversity in the sinuses leads to CRS would be extremely costly and impractical, while a case-control study that compares CRS individuals 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 microbiome instead?

Microbiota-altering treatments are safe and effective in other fields of medicine. Fecal microbiota transfers, or FMT for short, are highly effective at eradicating *C. diff.* from the gut[8]. FMT is beneficial in treating ulcerative colitis[9] and can improve signs and symptoms of extra-intestinal diseases, like atopic dermatitis or systemic lupus erythematosus[10,11]. It even increases response to immunotherapy for certain types of cancer[12]. 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) (**link to paper**). In this landmark study, we randomized nine patients to one of three interventions: SNMT, antimicrobial photodynamic therapy (aPDT), or a combination of the two.

Material for SNMT was endoscopically harvested directly from the middle meatus of healthy adults, all of whom screened negative for potentially transmissible diseases. The transfer material was then homogenized and applied under endoscopic vision directly into the affected patient's sinuses. aPDT is a non-antibiotic treatment that combines light with a photosensitizer to create free radicals that kill microbial cells[13]. It is performed under endsocopic vision using a fleixble balloon light cathether in under 5 minutes. We decided to test SNMT with and without aPDT to evaluate whether pretreating the sinuses before the transfer could enhance its efficacy.

Patients randomized to the aPDT arms were treated on days 0 and 7, while SNMT was done on days 7 and 8, 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 bacterial 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 how diverse a particular microbiome is at any given time – but did not demonstrate a permanent shift toward the donor's microbiome profile. However, we observed that, over time, their microbiome profiles changed compared to baseline. In other words, SNMT appears to transiently improve diversity and possibly "shift" the microbiome's composition.

Based on these promising results, we are now testing SNMT in a fully funded, double-blind, placebo-controlled randomized 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 trials will demonstrate that microbiota-altering therapies can influence inflammation in CRS. 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 question is whether we can simplify the process and store SNMT material for future use. However, these tentative questions depend on the trial's success.

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 eccentric idea is being seriously tested in a randomized trial. Regardless of the eventual outcome, we hope our research will inspire future generations to think outside the box and find creative solutions to a very complex problem.

References

1. Fokkens WJ, Lund VJ, Hopkins C, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. *Rhinology*. 2020;58(Suppl S29):1-464. doi:10.4193/Rhin20.600

2. Baguley C, Brownlow A, Yeung K, Pratt E, Sacks R, Harvey R. The fate of chronic rhinosinusitis sufferers after maximal medical therapy. *Int Forum Allergy Rhinol*. 2014;4(7):525-532. doi:10.1002/alr.21315

3. Cai S, Xu S, Lou H, Zhang L. Comparison of Different Biologics for Treating Chronic Rhinosinusitis with Nasal Polyps: A Network Analysis. *J Allergy Clin Immunol Pract*. Published online March 8, 2022. doi:10.1016/j.jaip.2022.02.034

4. Brown WC, Senior B. A Critical Look at the Efficacy and Costs of Biologic Therapy for Chronic Rhinosinusitis with Nasal Polyposis. *Curr Allergy Asthma Rep*. 2020;20(6):16. doi:10.1007/s11882-020-00910-y

5. 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):169-174. doi:10.2500/ajra.2010.24.3462

6. Ramakrishnan VR, Hauser LJ, Feazel LM, Ir D, Robertson CE, Frank DN. Sinus microbiota varies among chronic rhinosinusitis phenotypes and predicts surgical outcome. *J Allergy Clin Immunol*. 2015;136(2):334-342.e1. doi:10.1016/j.jaci.2015.02.008

7. Wagner Mackenzie B, Waite DW, Hoggard M, Douglas RG, Taylor MW, Biswas K. Bacterial community collapse: a meta-analysis of the sinonasal microbiota in chronic rhinosinusitis. *Environ Microbiol*. 2017;19(1):381-392. doi:10.1111/1462-2920.13632

8. Minkoff NZ, Aslam S, Medina M, et al. Fecal microbiota transplantation for the treatment of recurrent Clostridioides difficile (Clostridium difficile). *Cochrane Database Syst Rev*. 2023;4(4):CD013871. doi:10.1002/14651858.CD013871.pub2

9. Ding X, Li Q, Li P, et al. Long-Term Safety and Efficacy of Fecal Microbiota Transplant in Active Ulcerative Colitis. *Drug Saf*. 2019;42(7):869-880. doi:10.1007/s40264-019-00809-2

10. Kim JH, Kim K, Kim W. Gut microbiota restoration through fecal microbiota transplantation: a new atopic dermatitis therapy. *Exp Mol Med*. 2021;53(5):907-916. doi:10.1038/s12276-021-00627-6

11. Huang C, Yi P, Zhu M, et al. Safety and efficacy of fecal microbiota transplantation for treatment of systemic lupus erythematosus: An EXPLORER trial. *J Autoimmun*. 2022;130:102844. doi:10.1016/j.jaut.2022.102844

12. Davar D, Dzutsev AK, McCulloch JA, et al. Fecal microbiota transplant overcomes resistance to anti–PD-1 therapy in melanoma patients. *Science*. 2021;371(6529):595-602. doi:10.1126/science.abf3363

13. Biel MA, Sievert C, Usacheva M, Teichert M, Balcom J. Antimicrobial photodynamic therapy treatment of chronic recurrent sinusitis biofilms. *Int Forum Allergy Rhinol*. 2011;1(5):329-334. doi:10.1002/alr.20089