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RESEARCH NOTE

SinoNasal Microbiota Transfer to treat recalcitrant chronic rhinosinusitis: A case series

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KEYWORDS
chronic rhinosinusitis, experimental therapy, microbiome, microbiome therapy, mucus transplant, sinusitis

Key points

- SinoNasal Microbiota Transfer (SNMT) was safe with immediate benefit in all recipients, with sustained improvement in two of three recipients for up to 180 days.
- The addition of antimicrobial photodynamic therapy worsened chronic rhinosinusitis.
- These promising SNMT results warrant further study of safety and efficacy.

1 | INTRODUCTION

Chronic rhinosinusitis (CRS) is an inflammatory condition of the paranasal sinuses.[1] Recalcitrant CRS (or rCRS) occurs in <20% of patients[2] and has limited treatment options; new therapies are needed.

Microbiota transplantation is highly efficacious for treating recurrent *Clostridioides difficile* diarrhea.[3] In this

study, we tested a similar approach, SinoNasal Microbiota Transfer (SNMT), to restore the sinonasal microbiome. SNMT involves the endoscopic infusion of donated sinonasal mucus from a healthy donor into a rCRS recipient's sinuses. Treatment with antimicrobial photodynamic therapy (aPDT), a process used to sterilize the sinuses, was included as a pre-treatment to reduce the microbial load in diseased sinuses. We present a case-series study that investigated whether SNMT, with or without aPDT pre-treatment, reconstitutes the microbiota of rCRS patients and alleviates rCRS symptoms.

2 | METHODS

2.1 | Study design

This first-in-human study is a three-arm, open-label, randomized case series. Nine rCRS patients were randomized to (1) SNMT only, (2) aPDT only, or (3) aPDT + SNMT (Table 1). We included adult (18+ years) CRS patients who had persistent purulent discharge on endoscopy (modified Lund–Kennedy [MLK] score of >2) and elevated 22-item SinoNasal Outcome Test (SNOT-22) scores (>20 pts) despite maximal medical and surgical therapy. Sinus mucus donors were included if they had no signs of active sinus disease (section "Methods" in Supporting Information).

Following a screening visit, eligibility determination, and a baseline visit on day 0, the SNMT interventions were performed on days 7 and 8, and a repeat intervention was performed on days 21 and 22. aPDT was performed on days 0 and 7, followed by SNMT on days 7 and 8. The primary outcome was ascertained on day 30 post-intervention (Figure S1). The study protocol was approved by Health Canada (CTA control no. 227432) and the University Research Board (H18-022630). Informed consent was obtained from each participant. This study was conducted at St. Paul's Sinus Centre, a tertiary out-patient care center.

2.2 | SNMT intervention

Healthy donors, who were family and friends of recipients, were screened and included if they were asymptomatic and had negative findings for CRS on endoscopy. Donor sinonasal mucus was collected from the nasal passage and middle meatus under endoscopic guidance. A surgeon endoscopically suctioned mucus directly from the middle meatus and nasal cavity into a sterile suction trap. Once all visible mucus was collected, the middle meatus was washed with 10 mL of sterile saline and the fluid was aspirated. The donor mucus sample was homogenized using sterile, disposable rotor-stator homogenizer tips for 30 s and instilled into the affected recipient sinus cavity(ies) under endoscopic visualization. A cannula was placed into the affected sinus(es) with at least 5 mL of the donor mucus slowly sprayed/dripped into the affected cavities with the recipient's head in the dependent position. The recipients remained in this position for at least 15 min to facilitate transfer.

2.3 | aPDT

Affected sinus cavities were sprayed with a photosensitizer solution (0.1% methylene blue). A malleable intra-sinus balloon catheter was placed inside the affected sinus and inflated using 10 mL of saline. Light therapy was delivered via a catheter for 4 min.

2.4 | Outcome measures

The results of sinonasal endoscopy were recorded at each visit. Endoscopic videos were de-identified and sent for grading to an independent panel of three otolaryngologists who were blinded to the treatment allocation. An MLK score in the range of 0–12 was assigned to each video. The primary outcome was defined as a reduction in the MLK score of 1 unit and a change in the SNOT-22 score of 9 units or more, both considered clinically meaningful changes.[4,5] The sinonasal microbiome was assessed using whole metagenome sequencing of sinonasal mucus samples collected from both recipients and donors at each visit (section "Methods" in Supporting Information).

3 | RESULTS

3.1 | SNMT only

Of the three recipients in the SNMT-only arm, two showed improvement in MLK and SNOT-22 scores at 30 days post-intervention, with all three showing an improvement at 45 days (Figure 1A). Two recipients sustained these improvements for 180 days post-intervention (Figure 1B). None of the recipients received antibiotics.

3.2 | aPDT + SNMT

Two of four aPDT + SNMT recipients experienced improvement in their MLK score at 45 days, but this improvement worsened during follow-up (Figure 1A). Two

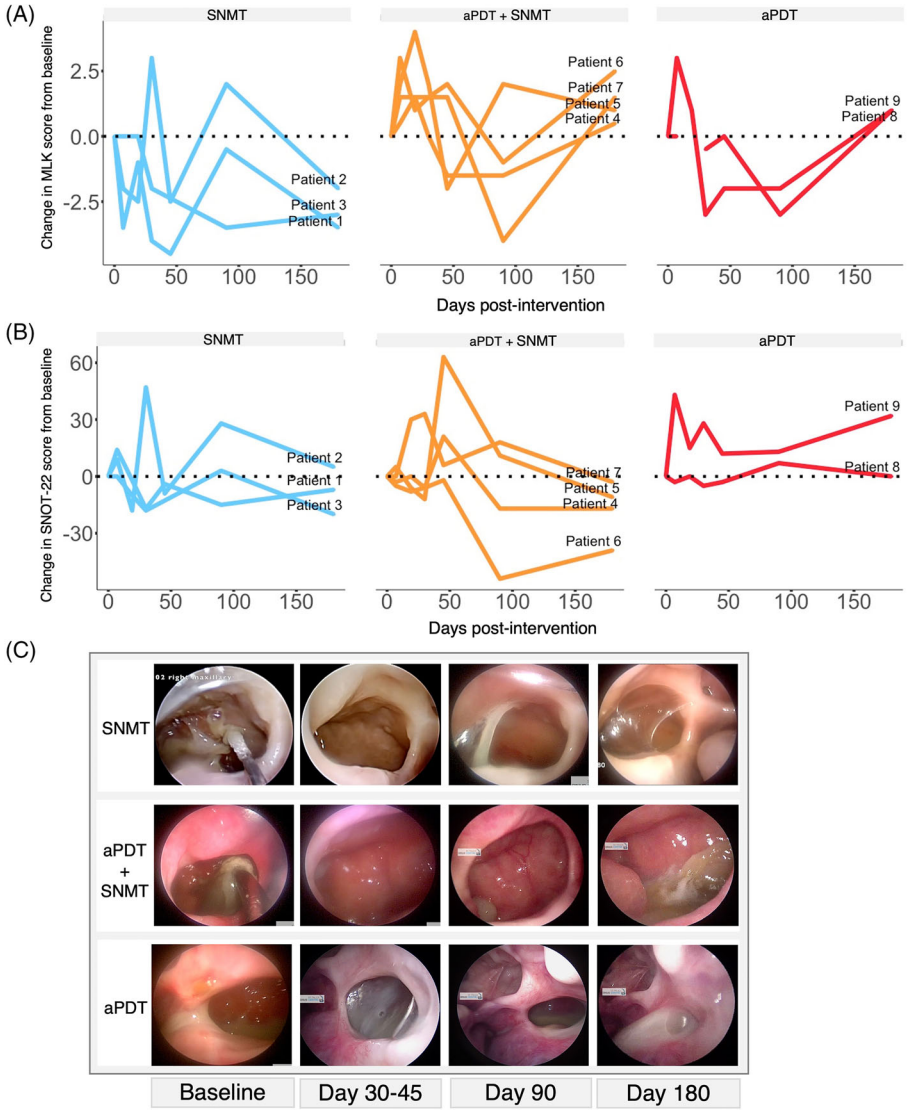

FIGURE 1 Changes in (A) modified Lund–Kennedy (MLK) scores measured as the change from baseline. A positive change depicts worsening of MLK scores, and a negative score depicts an improvement in MLK scores. MLK scores were assigned by three independent blinded assessors, and the mean value is shown. The blue line represents SinoNasal Microbiota Transfer (SNMT), the orange line represents SNMT + aPDT, and the red line represents antimicrobial photodynamic therapy (aPDT) recipients. (B) Changes in 22-item SinoNasal Outcome Test (SNOT-22). SNOT-22 scores are self-reported on a questionnaire by recipients at the start of the study visit. Data on the lines are graphed individually per recipient. (C) Endoscopic images of select representative patients in each of the trial arms at days 0 (baseline), 30, 90, and 180 post-intervention.

aPDT + SNMT arm recipients reported antibiotic usage over the study period (Table 1), including treatment for one sinus infection. SNOT-22 scores increased from baseline, but were not sustained, likely due to antibiotic therapy (Figure 1B).

3.3 | aPDT

The two aPDT-only recipients showed an improvement in MLK score between days 30 and 90 post-intervention. One recipient received antibiotics immediately after the intervention (Table 1). At 180 days, worsening MLK and SNOT-22 scores were observed (Figure 1A,B). Recipients reported discomfort associated with the aPDT intervention, possibly leading to higher MLK scores.

3.4 | Microbiome

There were no major differences in bacterial diversity between recipients and healthy donors' microbiota at baseline, apart from modest short-term increases in alpha diversity in the SNMT and aPDT + SNMT recipients. There

TABLE 1 Characteristics of study participants.

Recipient	Age	Duration of CRS disease (years)	Relevant comorbidities	Baseline MLK score	Baseline SNOT-22 score	Assigned intervention	Antibiotic usage in study (timepoint, indication, dosage)
1	59	15	Allergic rhinitis	7	17*	SNMT	–
2	59	14	Asthma	4	24	SNMT	–
3	53	10	Allergic rhinitis, asthma	5	31	SNMT	–
4	63	30	Allergic rhinitis, asthma	3	21	aPDT + SNMT	–
5	25	4	Ulcerative colitis	4	47	aPDT + SNMT	Day 45, cyst infection, doxycycline Day 90, mild conjunctivitis, tobramycin/dexamethasone Day 90, wisdom teeth, amoxicillin
6	54	8	Asthma, neuropathic pain	2	67	aPDT + SNMT	–
7	56	12	Allergic rhinitis, asthma	7	20	aPDT + SNMT	Day 30, sinus infection, doxycycline Day 60, sinus infection, cefuroxime
8	49	13	Allergic rhinitis	5	26	aPDT	–
9	67	30	Allergic rhinitis, asthma	3	31	aPDT	Day 7, sinus infection, doxycycline

Abbreviations: aPDT, antimicrobial photodynamic therapy; CRS, chronic rhinosinusitis; MLK, modified Lund–Kennedy; SNMT, SinoNasal Microbiota Transfer; SNOT-22, 22-item Sinonasal Outcome Test. *This was an early study protocol deviation.

was no obvious clustering of microbiota profiles between donors and recipients (Figure S2). Shifts in microbiome composition following SNMT intervention were observed. Some patients demonstrated tissue eosinophilia and high serum immunoglobulin E levels (Table S4).

3.5 | Safety

Overall, there were no adverse events. Recipients in the aPDT-only intervention group reported the highest overall pain and discomfort (visual analog for pain score) scores (section "Results" in Supporting Information).

4 | DISCUSSION

Collectively, SNMT alone led to sustained subjective and objective improvement in two of three recipients, suggesting that SNMT is a safe intervention that may clinically benefit rCRS patients. Interestingly, aPDT pre-treatment did not improve SNMT efficacy and was associated with worse outcomes. We observed shifts in the microbiota but not donor microbiota engraftment in response to SNMT. As this was a small case series, we have launched a randomized, double-blind, placebo-controlled trial to further test the efficacy of SNMT (vs. a saline placebo) for rCRS (ClinicalTrials.gov identifier: NCT05454072).

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

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SUPPORTING INFORMATION

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

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