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WILEY
A Comparison of the Bacterial Nasal Microbiome in Allergic Rhinitis Patients Before and After Immunotherapy

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Objectives/Hypothesis: Recent research has examined the nasal microbiome in rhinosinusitis and nondiseased states. Given immunologic alterations in allergic rhinitis (AR) and after allergen immunotherapy (IT), we evaluated the nasal microbiome in these conditions.

Study Design: Cross-sectional comparison.

Methods: In this cross-sectional study, nasal swabs for microbiome analysis were collected from three patient groups: IT-naïve AR patients, AR patients undergoing IT for greater than 12 months, and a control group without sinonasal inflammatory disease.

Results: Nasal swabs were successfully collected for 14 IT-naïve AR patients, 20 post-IT patients, and 17 controls. The α diversity showed a statistical difference in evenness but not in richness amongst samples, whereas the β-diversity was significantly different between groups. The microbiome did not appear to transition to a healthy microbiome composition.

Conclusions: β-diversity was found to be significantly different across the three groups, but the AR groups were found to be more similar to each other than to the controls. Although there is symptomatic improvement in the AR group undergoing IT, the microbiome does not appear to transition to a healthy microbiome composition.

Key Words: Microbiome, nasal, allergic rhinitis, immunotherapy, subcutaneous immunotherapy, sublingual immunotherapy.

Level of Evidence: 4

INTRODUCTION

The term human microbiome was coined in 2001 to describe the ecological community of commensal, symbiotic, and pathogenic microorganisms within and on the human body. Humans are inhabited by approximately equal parts bacteria to human cells, tens of trillions of bacteria that live on and within the human body. The Human Microbiome Project (HMP) was created in 2009 to characterize the human microbiome and to better understand the relationship between these microbial communities and human health and disease.

Research into the role of the microbiome in sinonasal disease is rapidly expanding. Some descriptive studies have characterized the phylogenetic makeup of the nasal microbiota in healthy and diseased subjects. Publications demonstrate a decrease in bacterial richness and diversity in chronic rhinosinusitis but an increase in bacterial diversity in allergic rhinitis (AR), supporting the theory that the nasal microbiome is reflective of sinonasal pathology.

AR is an immunoglobulin E-mediated response following exposure to inhalant allergens that results in inflammation. Current evidence demonstrates that 3 to 4 years of allergen immunotherapy (IT), which results in allergen-specific immune system tolerance, elicits a long-lasting benefit of up to 5 years posttreatment. AR is part of a Th2-predominant immunologic pathway. IT effectively decreases the IgE response and shifts the immune response toward regulatory T cells and cellular immunity. It follows that downregulation in the inflammatory pathway could influence bacterial biodiversity within the resident nasal microbiome.

In this study, we examined the bacterial nasal microbiome in two AR patient groups: 1) IT naïve patients and 2) AR patients following IT for over 1 year. These findings were compared to a control group without sinonasal pathology. This is the first study to analyze the changes that occur in the nasal microbiome of AR patients with IT. We hypothesized that the microbiome would shift as a result of IT intervention, with a transition toward a healthy microbiome.

MATERIALS AND METHODS

This cross-sectional study compared a sample of AR patients who had been treated with 1 year of IT (ARwIT), AR patients who were IT naïve (ARnIT), and a control group.
Patient Recruitment

Patients seen in the Emory University Sinus and Allergy Center were recruited to participate in this study between October 2017 and January 2018. Inclusion criteria for the AR groups were: ≥18 years and able to give informed consent and symptomatic AR confirmed by skin or in vitro testing. ARsIT patients had never received IT; ARwIT patients had received ≥1 year of IT. Exclusion criteria were: rhinosinusitis with/without polyposis, cystic fibrosis, autoimmune conditions affecting nasal mucosa, sinonasal tumor, aspirin-exacerbated respiratory disease, allergic fungal rhinosinusitis, and treatment with systemic or topical antibiotics in the preceding 4 weeks. IT patients were also excluded if a treatment break ≥1 month was observed. Control patients were ≥18 years and scheduled to undergo a transnasal approach for skull base surgery. Exclusion criteria for controls were: prior history of sinus surgery, actively secreting pituitary tumor, sinonasal symptoms, and treatment with systemic or topical antibiotics in the preceding 4 weeks. IT patients were also excluded if a treatment break ≥1 month was observed. Control patients were ≥18 years and scheduled to undergo a transnasal approach for skull base surgery. Exclusion criteria for controls were: prior history of sinus surgery, actively secreting pituitary tumor, sinonasal symptoms (infectious or allergic), and antibiotic use in the preceding 4 weeks. Clinical AR requires symptoms and positive allergy testing, so lack of symptoms excluded an AR diagnosis. Emory University Institutional Review Board approval was obtained, and all patients gave written informed consent. Patients were not compensated for study participation.

Swab Collection

Samples were collected from the middle turbinate/middle meatus under endoscopic visualization with DNA-free flocked swabs (Core Microbiome Sampling Protocol A–HMP Protocol #07-001) using a single swab per patient and rotating clockwise three times. Samples were collected in the clinic (AR patients) or in the operating room prior to administration of preoperative antibiotics or instrumentation of the nasal cavity (controls).

Sample Processing

Swabs were transported on dry ice and stored at −70°C. Samples underwent DNA extraction utilizing the MoBio PowerSoil DNA Isolation Kit (Cat #12888-50) (MO BIO Laboratories, Inc., Carlsbad, CA) and quantified via Quant-iT PicoGreen ds DNA Assay (Cat #P11496) (Thermo Fisher Scientific, Waltham, MA). Negative (molecular grade water) and positive (Zymo Microbial Community Standard [Cat #D6300], ZYMO Research, Irvine, CA) controls were used. Libraries were prepared using Illumina 16S Metagenomic Sequencing kit (Illumina, San Diego, CA) according to the manufacturer’s protocol. The V3–V4 region of the bacterial 16S rRNA gene sequences were amplified using the primer pair containing the gene-specific sequences and Illumina adapter overhang nucleotide sequences. Full-length primer sequences were: 16S Amplicon polymerase chain reaction (PCR) Forward Primer (5’TCCGTCGGCACGTCAGATGTGTATAAGAGACAGCCTACAGGN GGCGCWCGAG) and 16S Amplicon PCR Reverse Primer (5’GTCTCGTGGGCTCGAGATGTGTATAAGAGACAGCCTACAGGN GGCGCWCGAG) and 16S Amplicon PCR Reverse Primer (5’TCCGTCGGCACGTCAGATGTGTATAAGAGACAGCCTACAGGN GGCGCWCGAG) and 16S Amplicon PCR Reverse Primer (5’GTCTCGTGGGCTCGAGATGTGTATAAGAGACAGCCTACAGGN GGCGCWCGAG) and 16S Amplicon PCR Reverse Primer (5’TCCGTCGGCACGTCAGATGTGTATAAGAGACAGCCTACAGGN GGCGCWCGAG) and 16S Amplicon PCR Reverse Primer (5’TCCGTCGGCACGTCAGATGTGTATAAGAGACAGCCTACAGGN GGCGCWCGAG) and 16S Amplicon PCR Reverse Primer (5’TCCGTCGGCACGTCAGATGTGTATAAGAGACAGCCTACAGGN GGCGCWCGAG) and 16S Amplicon PCR Reverse Primer (5’TCCGTCGGCACGTCAGATGTGTATAAGAGACAGCCTACAGGN GGCGCWCGAG) and 16S Amplicon PCR Reverse Primer (5’TCCGTCGGCACGTCAGATGTGTATAAGAGACAGCCTACAGGN GGCGCWCGAG) and 16S Amplicon PCR Reverse Primer (5’TCCGTCGGCACGTCAGATGTGTATAAGAGACAGCCTACAGGN GGCGCWCGAG) and 16S Amplicon PCR Reverse Primer (5’TCCGTCGGCACGTCAGATGTGTATAAGAGACAGCCTACAGGN GGCGCWCGAG) and 16S Amplicon PCR Reverse Primer (5’TCCGTCGGCACGTCAGATGTGTATAAGAGACAGCCTACAGGN GGCGCWCGAG) and 16S Amplicon PCR Reverse Primer (5’TCCGTCGGCACGTCAGATGTGTATAAGAGACAGCCTACAGGN GGCGCWCGAG) and 16S Amplicon PCR Reverse Primer (5’TCCGTCGGCACGTCAGATGTGTATAAGAGACAGCCTACAGGN GGCGCWCGAG) and 16S Amplicon PCR Reverse Primer (5’TCCGTCGGCACGTCAGATGTGTATAAGAGACAGCCTACAGGN GGCGCWCGAG) and 16S Amplicon PCR Reverse Primer (5’TCCGTCGGCACGTCAGATGTGTATAAGAGACAGCCTACAGGN GGCGCWCGAG) and 16S Amplicon PCR Reverse Primer (5’TCCGTCGGCACGTCAGATGTGTATAAGAGACAGCCTACAGGN GGCGCWCGAG) and 16S Amplicon PCR Reverse Primer (5’TCCGTCGGCACGTCAGATGTGTATAAGAGACAGCCTACAGGN GGCGCWCGAG) and 16S Amplicon PCR Reverse Primer (5’TCCGTCGGCACGTCAGATGTGTATAAGAGACAGCCTACAGGN GGCGCWCGAG) and 16S Amplicon PCR Reverse Primer (5’TCCGTCGGCACGTCAGATGTGTATAAGAGACAGCCTACAGGN GGCGCWCGAG) and 16S Amplicon PCR Reverse Primer (5’TCCGTCGGCACGTCAGATGTGTATAAGAGACAGCCTACAGGN GGCGCWCGAG) and 16S Amplicon PCR Reverse Primer (5’TCCGTCGGCACGTCAGATGTGTATAAGAGACAGCCTACAGGN GGCGCWCGAG) and 16S Amplicon PCR Reverse Primer (5’TCCGTCGGCACGTCAGATGTGTATAAGAGACAGCCTACAGGN GGCGCWCGAG) and 16S Amplicon PCR Reverse Primer (5’TCCGTCGGCACGTCAGATGTGTATAAGAGACAGCCTACAGGN GGCGCWCGAG) and 16S Amplicon PCR Reverse Primer (5’TCCGTCGGCACGTCAGATGTGTATAAGAGACAGCCTACAGGN GGCGCWCGAG). Amplicon PCR was performed to amplify the template out of input DNA samples. Briefly, each 25 μL of PCR reaction contains 12.5 ng of sample DNA as input, 12.5 μL 2X KAPA HiFi HotStart ReadyMix (Kapa Biosystems, Wilmington, MA), and 5 μL of 1 μM of each primer. PCR reactions were carried out using the following protocol: an initial denaturation step performed at 95°C for 3 minutes followed by 25 cycles of denaturation (95°C, 30 seconds), annealing (55°C, 30 seconds) and extension (72°C, 30 seconds), and a final elongation of 5 minutes at 72°C. PCR product was cleaned up from the reaction mix with Mag-Bind RxnPure Plus magnetic beads (Omega Bio-Tek, Norcross, GA).

A second index PCR amplification was used to incorporate barcodes and sequencing adapters into the final PCR product. This was performed in 25-μL reactions, using the same master mix conditions as described above. Cycling conditions were as follows: 95°C for 3 minutes, followed by eight cycles of 95°C for 30 seconds, 55°C for 30 seconds, and 72°C for 30 seconds. A final 5 minutes elongation step was performed at 72°C. The libraries were normalized with Mag-Bind EquiPure Library Normalization Kit (Omega Bio-Tek) then pooled. The pooled library with ~600-bp insert size was validated using an Agilent 2200 TapeStation and sequenced (2 × 300 bp paired-end read setting) on the MiSeq (Illumina).

Data Processing

The 4pM pooled libraries were loaded into MiSeq with 20% PhiX. The data underwent quality filtering with an average of 97,000 reads per sample (range, 21,700–264,600 reads). The BaseSpace 16S Metagenomics app (San Diego, CA) performed 16S rRNA targeted amplicon sequencing using an Illumina-curated version of the May 2013 GreenGenes taxonomic database. Data were classified down to the species level using ClassifyReads, which is an implementation of the Ribosomal Database Project Classifier that was originally described by Wang et al. in 2007. Raw counts of each taxonomic level were used to create a normalized classification matrix. In ClassifyReads, species level assignment is given if the confidence in the read assignment is at least 98.24% or greater. Genus level information is only assigned if the confidence in the assignment is at least 99.65%. Because classification down to the genus level is more accurate, our analysis was performed of the genera data.

Statistical Analysis

Microbial diversity analyses were performed in R (R Foundation for Statistical Computing, Vienna, Austria) using the vegan package. α-diversity, which shows richness in quantity of species and evenness of a species within a sample, was calculated for each sample to determine differences in diversity between pre- and post-IT samples using a Shannon and Simpson index. Additionally, the Bray-Curtis dissimilarity (BCD) index was used to assess whether there was a significant difference in the bacterial composition between the three treatment groups, known as β-diversity. Differences in BCD by comparison type was assessed by Krouskal-Wallis test, and post hoc analysis was run using the Dunn test. R was used to examine the demographic
Fig. 1. Bacterial relative abundance amongst all samples within each group. (A) Bacterial relative abundance for allergic rhinitis group without immunotherapy intervention. (B) Bacterial relative abundance for allergic rhinitis group following immunotherapy intervention. (C) Bacterial relative abundance for the control group.
variables of age and smoking. The Kruskal-Wallis test was used to examine age along with Dunn’s test. Fisher exact testing was used to evaluate smoking status between the groups.

RESULTS

There were 14 patients in the ARsIT group, 20 patients in the ARwIT group (range, 1–4 years of IT; 14 subcutaneous IT, six sublingual IT), and 17 control patients analyzed. Thirty patients were female and 21 were male. Mean age in the ARsIT group was 34.8 years (range, 23–50 years), ARwIT group 47.15 years (range, 31–73 years), and controls 56.3 years (range, 26–87 years). There were 37 nonsmokers, five current smokers, and nine former smokers (Table I).

Age over 50 years has been associated with microbiome alterations at the phylum rank, and qualitative differences have been reported by smoking status6; therefore, age and smoking status were analyzed across study groups. Average age among the three groups was significantly different ($P < .05$). ARsIT mean age was lower than the ARwIT group ($P = .023$) and the control group ($P < .001$) by the Dunn test. There was no significant age difference between ARwIT and controls ($P = .189$). Smoking status was not significantly different across groups ($P = .7504$).

For all groups, the three most abundant genera, calculated from the average of the percentage present in each sample, were reported as a means of comparison. Within the ARsIT group, the most abundant genera were: Corynebacterium (37.1%), Staphylococcus (16.3%), Propionibacterium (10.7%). The dominant genus, Staphylococcus, ranged from 1.7% to 34.9%. The average number of species was 282.07 ± 89.12 (Fig. 1A).

For the ARwIT group, the three most abundant genera were: Staphylococcus (27.7%), Corynebacterium (18.7%), and Propionibacterium (6.6%). The dominant genus, Corynebacterium, ranged from 1.1% to 40.7%. One sample had Moraxella as the dominant genus, whereas the remaining samples had one of the three listed above. The average number of species was similar to the ARsIT group at 281.25 ± 102.40 (Fig. 1B).

For the controls, the three most abundant genera were: Staphylococcus (27.3%), Corynebacterium (26.3%), and Streptococcus (4.5%). The dominant genus, Corynebacterium, ranged from 0.7% to 90.6%. One sample had Prevotella as the dominant genera as opposed to one of the three mentioned above. The average number of species was lower for the controls at 219.88 ± 50 (Fig. 1C).

By examining the top 10 most abundant genera in each group, it was noted that each group had one to three genera not present in the other groups. The control group included Prevotella (3.1%), Veillonella (2.5%), and Haemophilus (2.2%). The ARsIT group included Anaerococcus (2.4%). The ARwIT group included Neisseria (5.4%) and Proteus (2.0%). Moraxella (ARwIT 2.0%; ARsIT 2.7%) and Ochrobactrum (ARwIT 2.8%; ARsIT 2.5%) were present in both AR groups but not within the most abundant genera in the control group (Fig 2).

The average Shannon diversity was 1.37 ± 0.39 for the ARsIT, 1.44 ± 0.68 for the ARwIT group, and 1.45 ± 0.68 for the control group. Kruskal-Wallis test revealed that the difference was not statistically significant ($P = .496$). The Simpson index, which is biased more toward evenness, was also calculated, and the Kruskal-Wallis test revealed statistical significance ($P = .021$). Although richness amongst samples was not significant, the distribution of species across groups was. Post hoc testing revealed that the

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A significant comparison was between the controls and the ARwIT groups ($P = .017$).

$\beta$-diversity was calculated using a BCD index across all three groups, showing a significant difference in community composition following PERMANOVA analysis ($P = .025$). The Dunn test demonstrated more similarity in nasal microbiome composition among AR patients than among control patients (Fig. 3). There was more compositional similarity within and between the two AR groups than there was within the control group or between the control group and either AR group. This highlights the variable makeup found in a healthy sinonasal microbiome. The three columns comparing the AR groups had the lowest level of average dissimilarity. This was found to be statistically significant in comparison to each column involving controls paired with an AR group. This shows that AR patients had a more similar microbiome to each other, regardless of IT status, in comparison to the control group.

In terms of species classification, the most common species in the control group was *Corynebacterium accolens*, *Corynebacterium accolens* in the ARsIT group, and *Staphylococcus aureus* in the ARwIT group. *S aureus* was present in the top six when taking all groups into consideration.

**DISCUSSION**

Prior studies have shown that AR patients, in general, have increased bacterial diversity in their microbiomes. In gastrointestinal disease, the dysbiosis theory is commonly invoked, postulating that bacterial diversity declines with infection and/or inflammation as the normal microbiome ecosystem is displaced. However, increased biodiversity has also been demonstrated in sputum from asthma patients versus controls. There are multiple hypotheses, such as hygiene and biodiversity, proposed to explain how human microbiota contribute to allergic disease and inherent tolerance to the immune system. The sinonasal mucosal microbiome has shown both increased and decreased biodiversity associated with pathologic inflammatory states. Although the specific mechanistic relationship between the human microbiome and disease is still elusive, it is evident that microbiome alterations are associated with disease, and further investigation is warranted.

Prior studies demonstrate that antibiotics and diet can contribute to dysbiosis, but few studies show how an intervention (i.e., surgery) can affect the nasal microbiome. One study by Jain et al. showed that microbiome shifts were unpredictable following sinus surgery but typically associated with increased richness of bacteria. A 2016 study by Hauser et al. investigated the ethmoid cavity and showed that bacterial burden was increased initially but that samples shifted back toward their baseline at six weeks.

Our study is novel in its examination of how a different intervention, IT, can impact the resident bacterial microbiome. Allergen IT generates an altered immune response to inhalant allergen, leading to symptomatic improvement over time. In this study, we hypothesized that IT-treated AR patients would have an altered microbiome compared to IT-naïve AR patients, potentially closer in composition to the control sample.

All patient groups had relatively high abundance of *Corynebacterium*, *Staphylococcus*, and *Propionibacterium*. *Corynebacterium* and *Staphylococcus* were the most abundant genera in all three patient groups, with the lowest mean percentage across all groups being 16.3% for the top two genera. The next highest abundance was 10.7% for any genus. It is possible that the less abundant genera are more meaningful drivers of a pathologic nasal microbiome.

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Fig. 3. $\beta$-diversity graphical results. (A) Boxplot depicting difference in $\beta$-diversity indices using pairwise comparisons. Letters A, B, and C represent statistical results from a Dunn’s test in which comparisons that do not share the same letter are statistically significant. (B) Principal coordinate (PCoA) analysis plot providing visual depiction of similarity and dissimilarity amongst all three groups. C = control; IT = allergic rhinitis undergoing immunotherapy; UT = allergic rhinitis immunotherapy naïve.
The α-diversity across samples did not demonstrate a significant group difference in richness but did show a difference in evenness, likely in reference to the variation in most abundant genera per sample. The β-diversity, which measures compositional distance, however, did show a significant difference. More specifically, this study showed that AR patients, regardless of IT treatment, had more similar microbiomes to each other than they did to the control population. Additionally, the control population was found to be highly dissimilar within its own cohort, which was not seen amongst the AR groups.

Although most studies report overall characteristics of microbiomes, such as diversity and abundance, there is not a consensus on predominant bacteria in either the healthy or diseased state. A recent study found the dominant organisms in their sample of AR patients (n = 50) to be Klebsiella, Escherichia coli, and S aureus, as opposed to Staphylococcus epidermidis in their healthy controls. Our study differed in our predominant bacteria in both AR groups, but we did show Staphylococcus to be predominant in all groups. For healthy controls, multiple studies have shown Propionibacterium acnes, S epidermidis, S aureus, and Corynebacterium to be prevalent. Our study did show both Staphylococcus and Corynebacterium genera to be predominant, and Propionibacterium was the 7th most common in our control samples. Although there is some alignment between our data and prior studies, it is possible that the lack of overall consensus is attributable to variability in sampling methods and analysis, demographic variables, or geographic differences.

There are some limitations to this study. In this cross-sectional design, our ability to match and control for demographic variables was limited. Demographic variables, such as smoking and age, have been shown to contribute to alterations in the nasal microbiome, although further characterization of this is yet to be ascertained. Our data did show a group difference in age, but smoking status was not different. It is unclear exactly how this may affect microbiome composition. Also, many of the AR patients were using topical sprays. IT-naive patients were using sprays as follows: six topical steroid, four topical antihistamine, three combination spray, and two not using sprays. For IT-treated patients: three topical steroid, eight topical antihistamine, nation spray, and two not using sprays. Ramakrishnan et al. followed five patients using topical steroid spray or topical mupirocin. Two patients were unaffected by topical therapy, but three patients had altered microbial diversity persisting at least 2 weeks following treatment. Conclusions from this are difficult because it is a single study with a small sample size, and mupirocin may be expected to change bacterial composition. The etiology of the microbial shift is likely multifactorial. Therefore, topical sprays may affect the microbiome, and further study is warranted. The exclusion criteria accounted for recent antibiotic use, prior sinus surgery, and diagnosed sinonasal pathology. A final limitation is the possibility that the microbiome does not maintain stability over time and we are capturing one time point in this study.

Future directions of this work include longitudinal follow-up of AR patients during the IT treatment period to allow for serial repeated measures of the nasal microbiome status within each patient over time.

CONCLUSION
This study evaluated the change in the bacterial nasal microbiome that occurs in response to IT in AR patients. There is a significant difference in β-diversity or relative microbial diversity between samples. AR patients, regardless of status of IT treatment, had more similar microbiomes to each other than they did to controls. The bacterial nasal microbiome in AR patients with at least 1 year of IT does not transition to a similar composition to controls. At this time, it is not clear whether this change may occur over a longer treatment period or if a transition in the AR nasal microbiome does not occur, in which case alterations in the nasal microbiome would not be seen as an underlying factor in the clinically reported symptomatic improvement with allergen IT.

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