Oral bacterial diversity correlates with pulmonary function in adults with cystic fibrosis on CFTR modulator therapy.

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Background, methods, and objective

Despite highly effective modulator therapies (HEMT) for people with cystic fibrosis (pwCF), lung infections persist and contribute to the decline of pulmonary function. Lung infections are often polymicrobial with "classic CF pathogens" such as *S. aureus* and *P. aeruginosa,* but also often involves anaerobic bacteria likely from aspirated oral saliva. The contribution of oral derived bacteria toward disease pathophysiology and pulmonary function is underexplored. As such, we hypothesized that the oral microbiota may be associated with pulmonary outcomes in CF.

Methods:

As part of an ongoing multi-center cohort study, we conducted a preliminary cross-sectional analysis of 85 pwCF on HEMT. For this analysis, lung function data and saliva samples were collected at baseline to explore the association of the oral microbiome and pulmonary function. To characterize the oral microbiome, total DNA was extracted from unstimulated saliva and the V3-V4 region of the bacterial 16S rRNA gene was sequenced using Illumina technology. Lung function was measured by spirometry and presented as % predicted FEV1 (ppFEV1) and FEV1/FVC. In addition, demographic and clinical characteristics were also obtained from each participant.

Characteristics of the study population

Characteristic	N = 85
Age (y), Mean (SD)	18.7 (5.3)
Age category, n (%)	
12-17 yo	41 (48.2)
18-30 yo	44 (51.8)
Sex - Female, n (%)	36 (42.4)
ppFEV1, Mean (SD)	97.4 (18.6)
FEV1/FVC (L), Mean (SD)	0.8 (0.1)
Chronic antibiotics, n (%)	71 (83.5)
Inhaled corticosteroids, n (%)	22 (25.9)
Sputum culture, n (%)	65 (76.5)
Single infection, n (%)*	26 (40.0)
Co-infection, n (%)*	16 (24.6)
Negative, n (%)*	23 (35.4)
Proton pump inhibitors, n (%)	25 (29.4)

Table 1. Data representing all 85 participants with Cystic Fibrosis on elexacaftor-tezacaftor-ivacaftor or ivacaftor.

- Proportions based on total sputum cultures

Oral bacterial dysbiosis is associated with chronic use of antibiotics

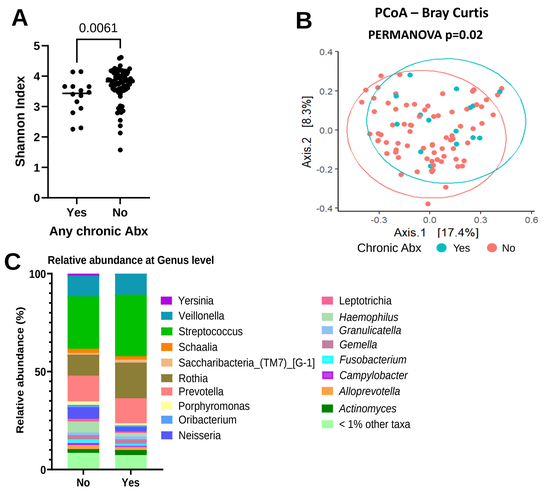

Figure 1. (A) Comparison of alpha diversity Shannon index by use of any chronic antibiotic using Mann-Whitney test. (B) Principal coordinate analysis based on Bray Curtis distance by use of any chronic antibiotic. (C) Relative abundance of taxa at genus taxonomic level by chronic antibiotic use.

Pulmonary infection is associated with oral bacterial dysbiosis

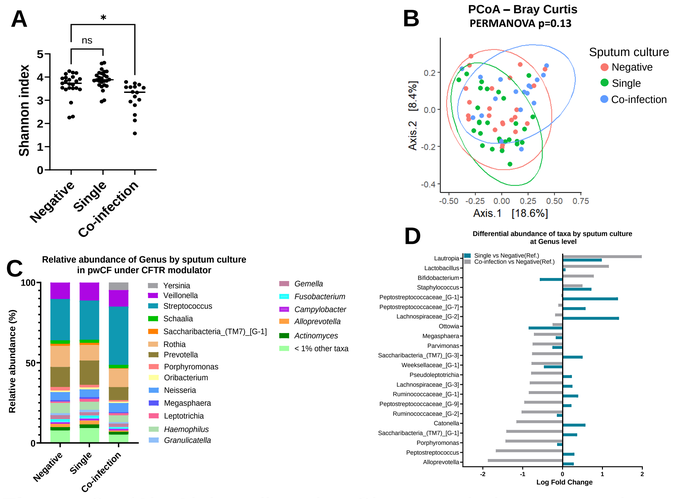

Figure 2. (A) Alpha diversity Shannon index comparison by Single/Co-infection in the sputum culture using Mann-Whitney test. (B) Principal coordinate analysis based on Bray Curtis distance by sputum single/Co–infection. (C) Relative abundance of taxa at genus taxonomic level by single/co-infection in the sputum. (D) Differential abundance analysis (ANCOM-BC2) at genus level.

Oral bacterial diversity positively correlates with ppFEV1 in adults

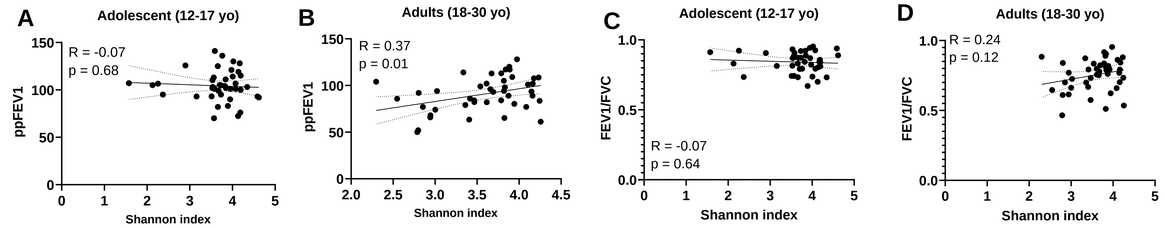

Figure 3. Pearson correlation between ppFEV1 and Shannon index in adolescents (A) or adults (B). FEV1/FVC ratio Pearson correlation with Shannon index in adolescents (C) or adults (D).

Oral bacterial community structure is associated with pulmonary function in adults

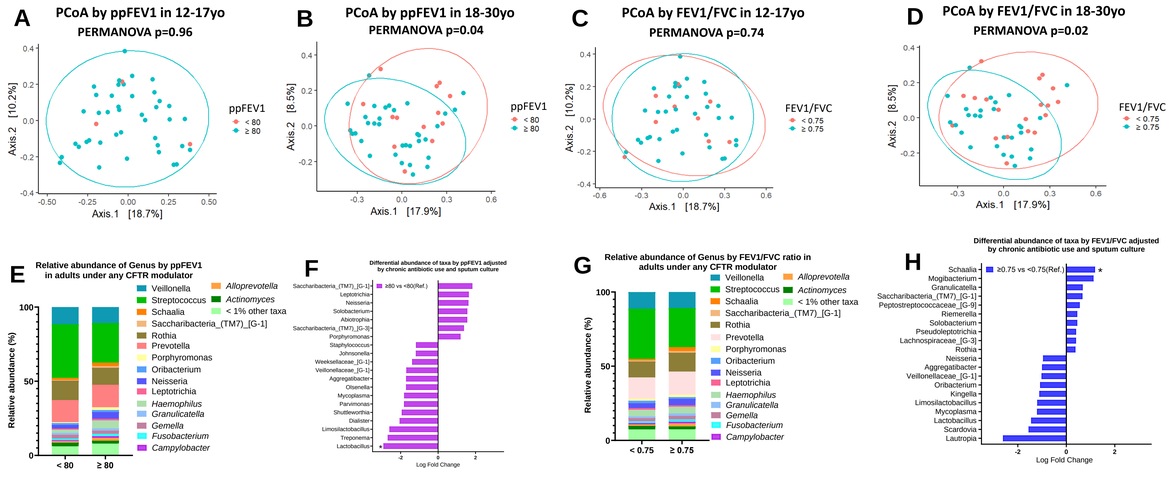

Figure 4. Principal coordinate analysis based on Bray Curtis distance comparing beta diversity bacterial community structure by ppFEV1 in (A) adolescents and (B) adults, and FEV1/FVC ratio (C) adolescents and (D) adults. Relative abundance of taxa at genus taxonomic level by (E) ppFEV1 and (G) FEV1/FVC ratio. Differential abundance analysis (ANCOM2) adjusted by chronic use of any antibiotic and sputum culture by (F) ppFEV1 and (H) FEV1/FVC.

Conclusions

- Oral bacterial diversity and microbial composition is associated with pulmonary function in adults with CF on HEMT, but not in adolescents.
- Pulmonary co-infection (sputum culture) is associated with oral bacterial diversity and community composition in pwCF on HEMT.
- Use of any chronic antibiotic is associated with lower oral bacterial diversity and changes in microbial composition in pwCF on HEMT.
- Pulmonary co-infection (compared to single-infection) is associated with lower oral bacterial diversity.

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