The association of oral and stool microbiome with bronchiolitis obliterans syndrome after hematopoietic cell transplantation

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Background

- Hematopoietic cell transplantation (HCT) is a potentially curative procedure indicated for high-risk hematalogic malignancies
- Graft-versus-host-disease (GVHD) is a major source for non-relapse morbidity and mortality in allogenic HCT recipients
- Lung GVHD presents as bronchiolitis obliterans syndrome (BOS), a severe lung disease
- BOS is diagnosed by progressive small airways obstruction in the absence of infection
- NIH criteria are very stringent and may miss early cases
- On the other hand, a more flexible set of criteria (BOS 0p), which only requires a 10% fall in forced spirometry, has a 70% false positive rate due to the low prevalence of BOS
- Biomarkers that are associated with early BOS can minimize false positives and hasten the diagnosis of BOS.

Methods

Study Design

- 1 year observational study of biomarkers in HSCT Recipient with GVHD
- Planned accrual of new diagnoses of (50 planned)
  - Lung GVHD (BOS) – 20 patients
  - BOS 0p (subclinical decline) – 20 patients
    - Expect 30% to actually have BOS based on prior data (preBOS) Remaining would be false positive
  - cGVHD controls – 10 patients

Analysis of the Microbiome

The α-diversity, β-diversity, and abundance were assessed in each group. Bacterial 16s RNA sequencing was utilized to determine the taxa presented in the results.

- α-diversity compares a single specimen amongst two groups of interest.
- β-diversity compares community composition amongst two groups.

Hypothesis

The oral and gut microbiome will in patients with BOS and preBOS will be distinct from those patients who have transient or no lung impairment

Results

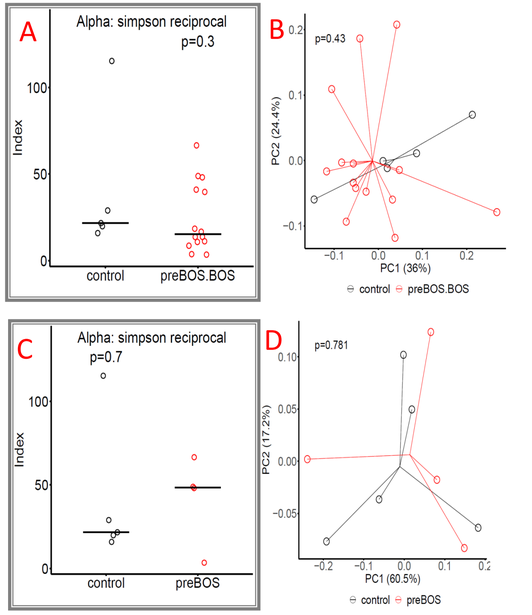

Figure 1. The following figures illustrate an insignificant statistical difference in α-diversity & β-diversity in the oral microbiome.

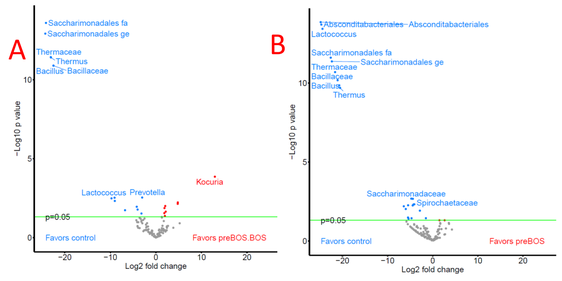

Figure 2. Abundance across all groups is not statistically significant. The only exception is between the control vs. pre-BOS where a notable depletion of the microbiome is appreciated in the pre-BOS group.

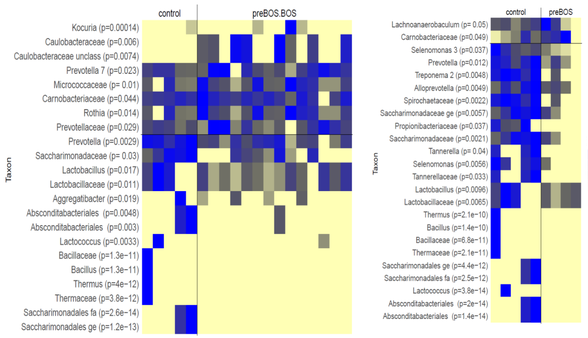

Figure 3. The heatmaps pictured illustrate the same outcomes from Figure 2. Abundance does not show a statistically significant difference amongst most groups. The only exception is between the control vs. pre-BOS where a notable depletion of the microbiome is appreciated in the pre-BOS group. Conclusions drawn from these small sample sizes should be interpreted with caution.

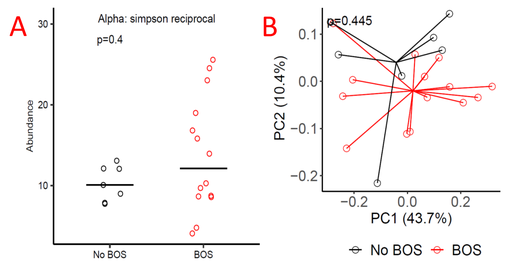

Figure 4. The following figures illustrate an insignificant statistical difference in α-diversity & β-diversity in the gut microbiome. Relative abundance is not statistically different; however, there is a small difference in species composition between BOS & non-BOS cases.

Discussion

- Depletion of the oral microbiome is associated with diagnosis of BOS and preBOS, but α- and β-diversity were not.
- Recent studies have found strong associations between pre-HCT microbial depletion and post-HCT fatal lung injury in children (Zinter et al, Blood 2021)
- However, observational designs may mischaracterize the causal direction between inflammation and microbial depletion
- Inducing experimental inflammation does not lead to short-term changes in abundance or diversity in preclinical models (Pantaleon et al, Ann ATS 2021)
- Future work from the complete cohort will analyze subgroup effects, control for antibiotic use, and correlate with nasopharyngeal inflammation.
- A larger study is necessary to systematically evaluate other microbial compartments beginning at a common time point and to correlate the kinetics of microbial depletion with the kinetics of inflammatory changes

References

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