

RESEARCH NOTE

Dysbiosis in aspirin-exacerbated respiratory disease

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KEYWORDS

aspirin-exacerbated respiratory disease, asthma, chronic rhinosinusitis, dysbiosis, microbiome, nasal polyposis, nasal polyps

Aspirin-exacerbated respiratory disease (AERD) is a distinct subtype of severe chronic rhinosinusitis (CRS) characterized by nasal polyposis, difficult-to-treat asthma, and adverse reactions to nonsteroidal anti-inflammatory drugs (NSAIDs). Although microbiome dysbiosis has been described in heterogeneous populations of individuals with CRS, it has not been well evaluated in a defined cohort with AERD.

SUBJECTS AND METHODS

By swabbing the superior portion of the inferior turbinates and sequencing the hypervariable regions of 16S ribosomal RNA, we interrogated the nasal microbiome of 17 subjects with AERD compared to 20 healthy controls (HCs).

RESULTS

AERD subjects and HCs showed no differences in basic demographics. Reflecting a high burden of upper and lower airway disease, AERD subjects reported on average

3 prior sinus surgeries, a 22-item Sino-Nasal Outcome Test (SNOT-22) score of 30.2, and an asthma control test (ACT) score of 19.9 (ie, borderline control). AERD samples had the highest relative abundance (RA) of the following genera: *Moraxella* (10.83%), *Corynebacterium* (8.66%), *Pseudomonas* (7.23%), *Staphylococcus* (7.08%), *Sphingomonas* (6.47%), *Streptococcus* (6.28%), *Propionibacterium* (5.99%), and *Eikenella* (5.95%). HC samples had the highest RA of *Corynebacterium* (27.25%), *Propionibacterium* (7.57%), *Bacteroides* (7.14%), *Prevotella* (6.69%), and *Staphylococcus* (5.53%). Although difference in mean RA of *Eikenella* did not meet statistical significance at the population level, differences between individual subjects were more striking. Six AERD subjects had >10% RA of *Eikenella corrodens*, with 2 exceeding 25%. Comparatively, there was no HC with >10% RA of *Eikenella corrodens* ($p = 0.005$). In contrast, 14 HCs had >10% RA of *Corynebacterium* spp. compared to 4 AERD subjects ($p = 0.008$).

Demonstrating a reduction in bacterial diversity, AERD subjects had fewer species per sample and lower Shannon Diversity indices ($p = 0.048$). In clustering of subjects according to relative abundances (Fig. 1), AERD

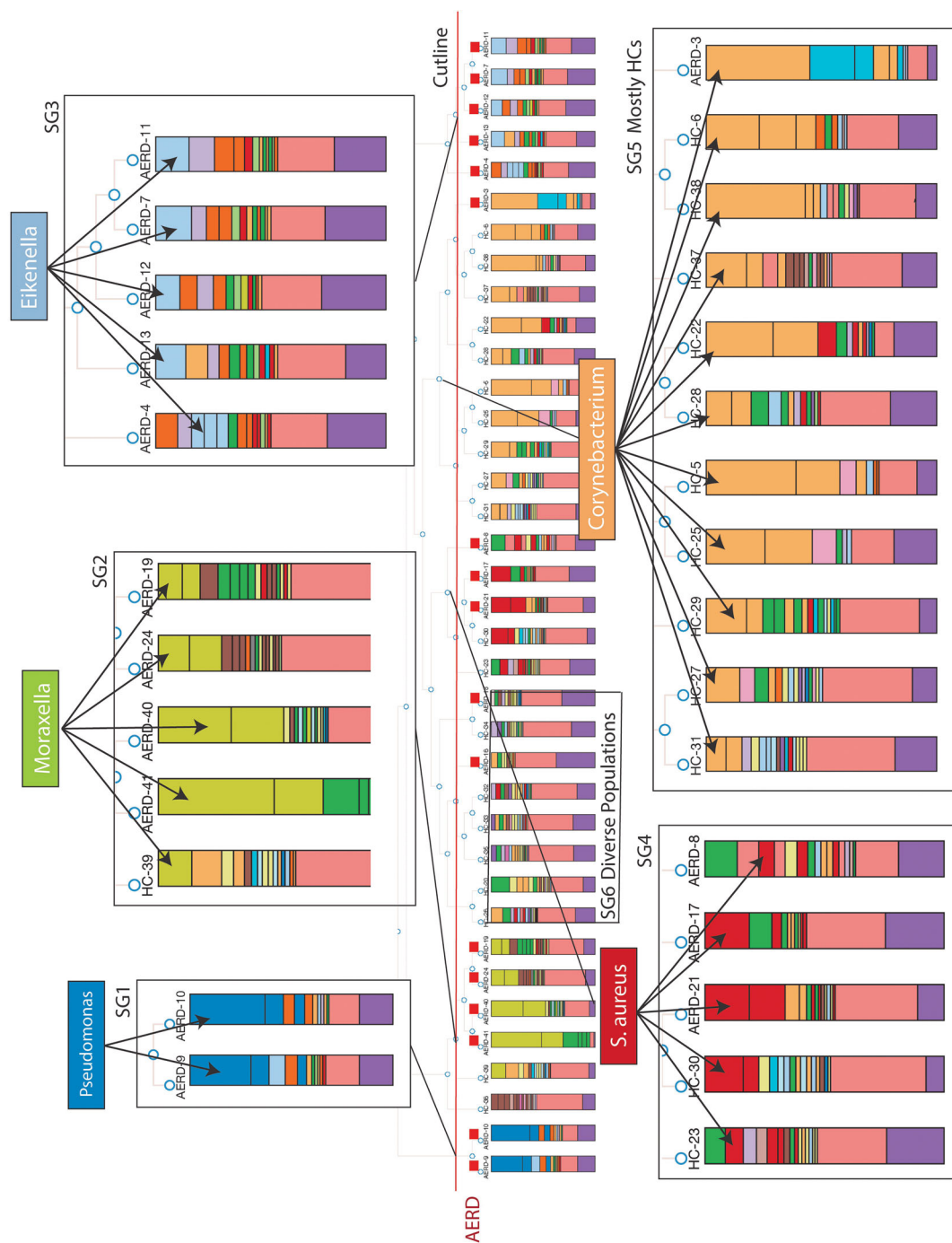


FIGURE 1 Hierarchical clustering dendrogram by genus. Based on the cutline, SGs were identified and described in the text. HCs = healthy controls; SG = subgroup

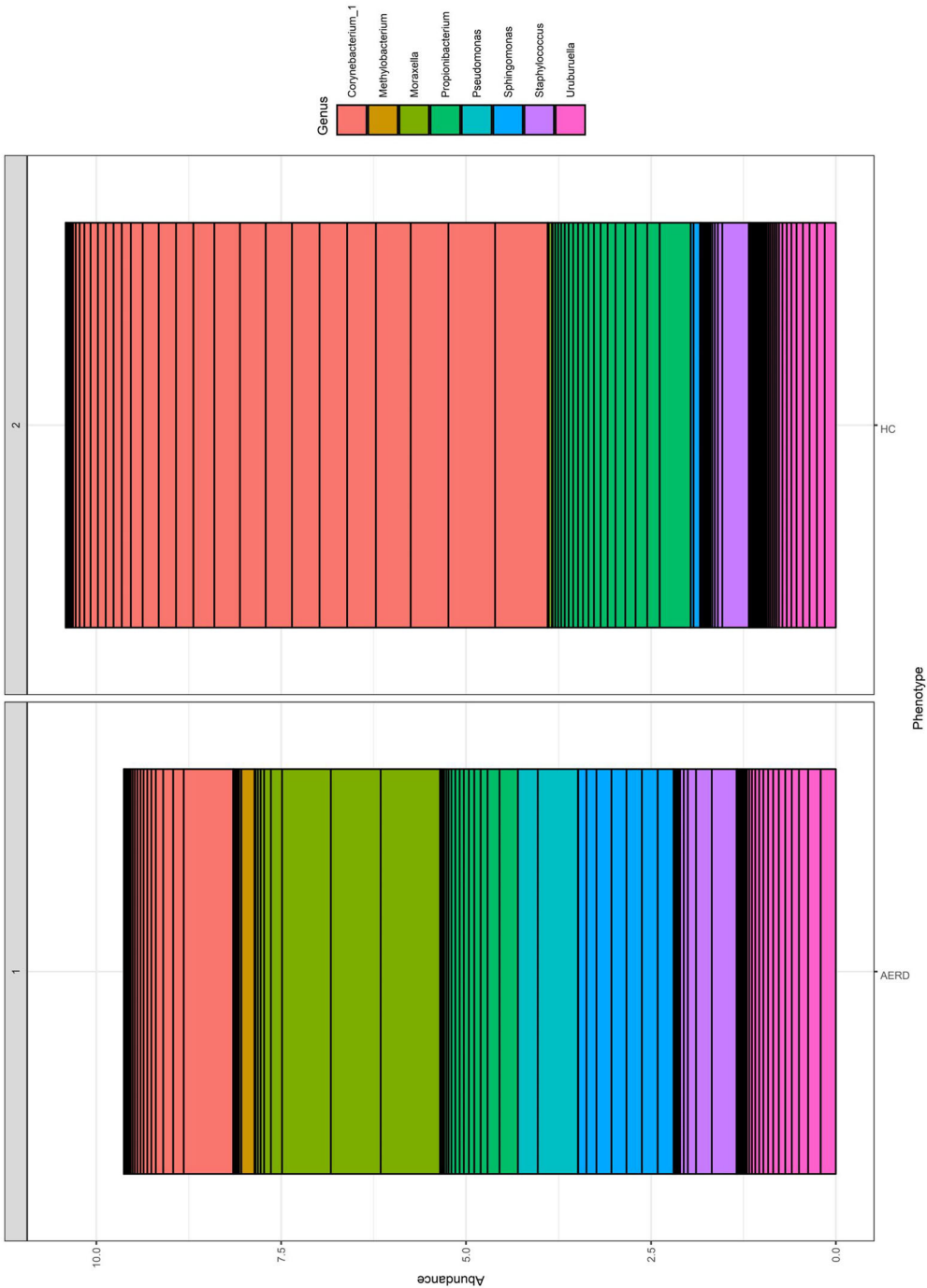


FIGURE 2 OTU analysis using the metagenomics R package (R Foundation for Statistical Computing, Vienna, Austria; <https://www.r-project.org/>). Raw reads were used to assign taxonomy, showing a notable increase in reads aligning to *Corynebacterium* and *Propionibacterium* among HCs. Alternatively, reads aligning to pathogenic bacteria were higher in AERD, including *Moraxella*, *Pseudomonas*, *Sphingomonas*, etc. AERD = aspirin-exacerbated respiratory disease; OTU = operational taxonomic unit

subjects separated from HCs based primarily on a loss of *Corynebacterium*. Most AERD samples clustered into 1 of the 4 following subgroups based on an overabundance of 1 of the following species: *Eikenella corrodens*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. Reflecting the heterogeneity of microbiomes, these clusters were not exact because 2 of 5 samples in the *S. aureus* cluster and 1 of 5 in the *M. catarrhalis* cluster were healthy controls. Alternatively, 1 of 11 samples in the *Corynebacterium* cluster was an AERD subject. The remaining HCs ($n = 9$) and AERD subjects ($n = 2$) had very diverse bacterial populations. Nonetheless, we can see clear patterns of dysbiosis in AERD subjects. Operational taxonomic units (OTUs), which are used to computationally group bacteria based on similarity of 16S raw sequence reads, found similar results (Fig. 2), as did a phylogenetic tree analysis based on OTUs.

DISCUSSION

AERD microbiomes reflect dysbiosis with loss of diversity, particularly *Corynebacterium* and other commensal bacteria, and high relative abundance of pathogenic species. Supportively several studies have revealed similar dysbiosis in CRS with loss of diversity including commensals.^{1,2} Severe CRS subtypes such as cystic fibrosis (CF) demonstrate more profound dysbiosis when compared to CRS.³ Whether the loss of *Corynebacterium* and other commensals is due to disease processes or repeated treatment with antibiotics remains unknown, but this perhaps warrants further investigation.

The overabundance of *Eikenella corrodens*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa* noted in AERD microbiomes, which all fall within the Proteobacteria phylum and have similar microbial characteristics, may have comparable effects on the host immune response in AERD. Although the prevalence and importance of *Pseudomonas aeruginosa* and *Moraxella catarrhalis* in CRS has been well-described and is often observed clinically, the increased prevalence of *Eikenella corrodens* in AERD was unexpected. Described as foul smelling and known to form biofilms, *Eikenella corrodens* can cause recurrent and persistent head and neck infections that are often polymicrobial and run an indolent course.⁴⁻⁶ This finding requires validation longitudinally and in larger AERD populations. Our data suggests that treatment aimed at *Eikenella corrodens* and potentially biofilm formation may warrant investigation as a therapeutic option for some AERD subjects.

Limitations of this study include sample site selection, relatively small sample size, lack of a disease-specific

control (other CRS phenotypes), and cross-sectional study design. Although studies have not demonstrated significant differences in microbial diversity or abundance in sampling from the inferior turbinate vs the middle meatus, there is potential that the portion of the inferior turbinate sampled was not entirely reflective of the nasal and/or sinus cavities.⁷ Any variability in microbiome within the AERD cohort must be considered in context of disease treatment, notably prior treatment with antibiotics (often frequent and/or prolonged) directly impacting sinonasal microbiota, aspirin desensitization, corticosteroids, and surgeries. Although patients with recent use of antibiotics and systemic corticosteroids were excluded, there might be a lingering effect of repeated or relatively recent treatment, which is common in patients with AERD. The limited sample size makes its generalizability to larger populations unknown. Finally, given its cross-sectional design, we also do not know the stability of our findings over time.

In summary, AERD microbiomes demonstrate replacement of diverse, commensal bacteria populations with low-diversity microbiomes overrun with nonresident pathogenic bacteria. More than one-third of AERD patients had increased abundance of a pathogenic, biofilm-capable bacterium, *Eikenella corrodens*, which has not been previously reported. Further investigation is warranted to determine whether dysbiosis in AERD is a driving factor disease or a consequence of the inflammatory milieu and prior treatment(s).

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