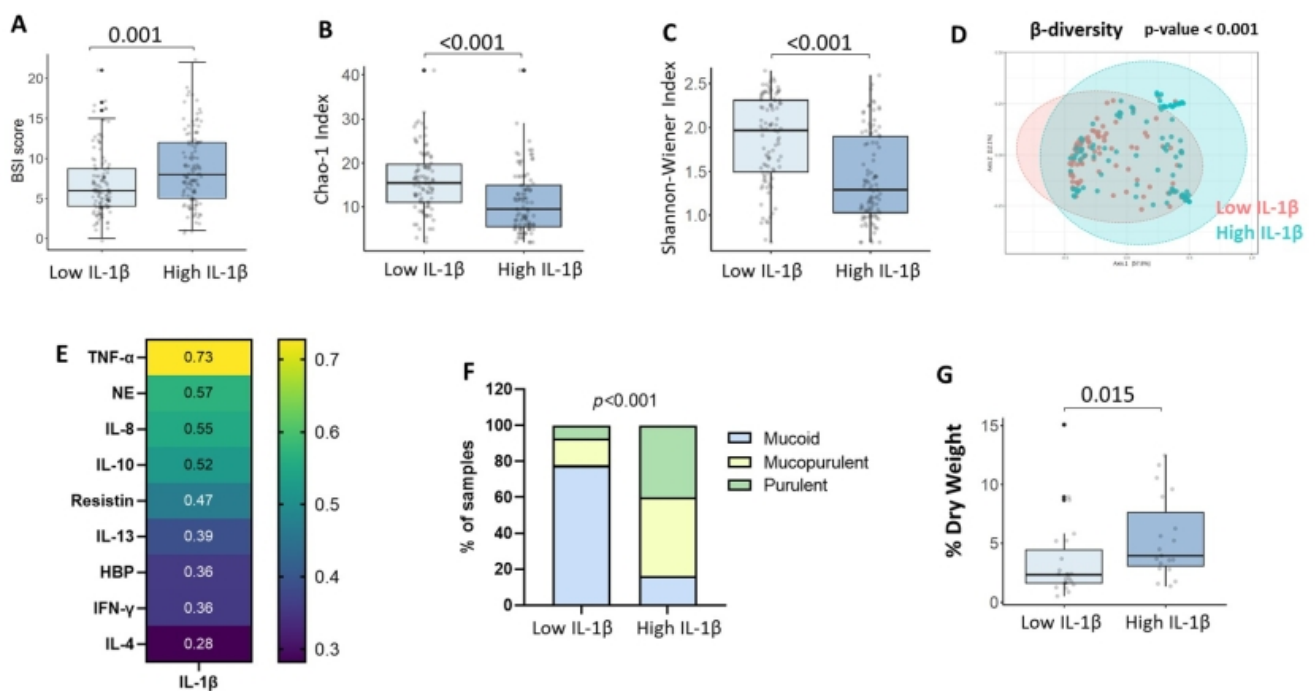


## The Relationship Between Airway Interleukin-1 Beta, Microbial Dysbiosis and Mucus Hyperconcentration in Bronchiectasis: The EMBARC-BRIDGE Study

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**RATIONALE:** Mucus hyperconcentration and impaired mucociliary clearance are central features of bronchiectasis. Inflammation and infection are believed to be the key mediators of impaired mucociliary clearance. IL-1 $\beta$  is a key regulator of inflammatory responses and directly triggers mucus production and hyperconcentration in cystic fibrosis. The role of IL-1  $\beta$  in bronchiectasis has not been investigated. The aim of this study was to investigate the relationship between sputum IL-1 $\beta$  levels and disease severity, the microbiome, inflammation, and mucus properties in an international bronchiectasis cohort. **METHODS:** Sputum samples from 269 patients with stable bronchiectasis were collected at three European centres (Dundee, Milano, Barcelona) as part of a European observational cohort study NCT03791086. IL-1 $\beta$  levels were measured by Meso Scale Discovery (MSD) assay in sputum supernatant. Patients were stratified in two groups according to the IL-1 $\beta$  median value (designated High and Low for analysis). Disease severity was evaluated using the bronchiectasis severity index, microbiome by 16S rRNA sequencing and Th1, Th2 and Th17 inflammatory mediators were evaluated by MSD assay. Mucus properties were determined by rheology in an independent cohort of 51 patients. **RESULTS:** Patients with high sputum IL-1 $\beta$  had more severe disease (Fig.1A), a Proteobacteria dominated microbiome, lower microbial diversity (Fig.1B-D) and significantly higher Th1, Th2 and Th17 inflammatory mediators (TNF- $\alpha$ , IFN- $\gamma$ , IL-10, IL-4, IL-13, IL-8, resistin, neutrophil elastase, heparin binding protein) than patients with low sputum IL-1 $\beta$  (all  $p < 0.0001$ ). Sputum IL-1 $\beta$  levels also showed linear correlations with all these inflammatory mediators (Fig.1E). IL-1 $\beta$  was related to sputum purulence (84% mucopurulent or purulent in the high group vs 22.2% in the low group; Fig.1F) and increased mucus solid content measured by the percentage of dry weight (Fig.1G) indicative of mucus dehydration. IL-1 $\beta$  was also associated with the viscoelastic properties of mucus. Specifically, it was associated with elastic ( $G'$ ) ( $\rho = 0.43$ ,  $p = 0.002$ ), viscous ( $G''$ ) ( $\rho = 0.48$ ,  $p = 0.0004$ ) and complex ( $G^*$ ) moduli ( $\rho = 0.46$ ,  $p = 0.0006$ ), and with damping factor ( $\rho = 0.32$ ,  $p = 0.02$ ) by rheology. **CONCLUSIONS:** IL-1 $\beta$  is strongly related to microbial dysbiosis and mucus dehydration in patients with bronchiectasis. **Funding:** European Respiratory Society through the EMBARC2 consortium and a Long-term research fellowship to LP.



**Figure 1. Stratification of patients according to IL-1 $\beta$  levels.** Analysis of the association between (A) Bronchiectasis Severity Index score (BSI; Mann-Whitney test,  $n=269$ ), (B) Chao-1 and (C) Shannon-Wiener diversity index (Mann-Whitney test,  $n=210$ ), (D)  $\beta$ -diversity analysis (PERMANOVA test,  $n=210$ ), (E) inflammatory mediators (Mann-Whitney test,  $n=269$ ), (F) Murray Chart ( $\chi^2$  test,  $n=51$ ) and (G) percentage of sputum dry weight (Mann-Whitney test,  $n=42$ ) and sputum IL-1 $\beta$  levels.

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