

Clinical Relevance of the Pulmonary Mycobiome in Non- Cystic Fibrosis Bronchiectasis: The CAMEB Study

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Clinical Relevance of the Pulmonary Mycobiome in Non-Cystic Fibrosis Bronchiectasis: The CAMEB Study Introduction: The role for fungi in chronic pulmonary diseases such as asthma and cystic fibrosis is emerging however no investigation to date has addressed this in non-CF bronchiectasis. We performed, to our knowledge, the largest investigation of the pulmonary mycobiome across three countries (Singapore, Malaysia and Scotland) and two populations (Asian and European). Recruited patients were part of the CAMEB study: a cross-sectional Cohort of Asian and Matched European Bronchiectasis patients. Methods: Stable bronchiectasis patients (N = 238) from Singapore (N=124), Malaysia (N=14) and Scotland (N=100) were recruited as participants of the CAMEB study. Non-diseased controls (N=10) were also recruited in Singapore. We performed mycobiome analysis in representative patient sputum in addition to specific qPCR for detection of various *Aspergillus* species. Sputum galactomannan (GM), *Aspergillus*-specific IgE (sIgE) measurements for *A. fumigatus* and *A. terreus*, Thymus and Activation Regulated Chemokine (TARC) levels and Anti-*Aspergillus* IgG levels were measured in patient serum and associated clinical data was collated. Results: Analysis of the bronchiectasis mycobiome revealed the presence of distinct fungal genera including: *Aspergillus*, *Issatchenkia*, *Wickerhamomyces*, *Simplicillium*, *Cryptococcus*, *Clavispora*, *Botrytis*, *Alternaria*, *Trametes* and *Phlebia*. Speciation by qPCR revealed the presence of *A. fumigatus* and *A. terreus* only. While both Asian and European populations had patients with either or both fungi, *A. fumigatus* was more common in Asians whilst *A. terreus* dominated in Europeans. The presence of *A. terreus* was associated with increased exacerbations. High occurrence of *Aspergillus* sensitization and serologic allergic bronchopulmonary aspergillosis (sABPA) were found in both cohorts and associated with poorer lung function, increased exacerbations and greater disease severity. Conclusion: We demonstrate for the first time that the pulmonary

mycobiome in bronchiectasis is distinct and has clinical relevance. Screening for *Aspergillus*-associated clinical disease should be considered even in bronchiectasis patients who appear stable. Funding: This research is supported by the Singapore Ministry of Health's National Medical Research Council under its Transition Award (NMRC/TA/0048/2016) (S.H.C) and the Changi General Hospital Research Grant (CHF2016.03-P) (T.B.L). C.F.T. has received research support from the Singapore Ministry of Education Academic Research Fund, the Singapore Immunology Network, and the Biomedical Research Council (BMRC) (N-154-000-038-001, R-154-000-404-112, R-154-000-553-112, R-154-000-565-112, R-154-000-630-112, R-154-000-A08-592, R-154-000-A27-597, SlgN-06-006, SlgN-08-020, BMRC/01/1/21/18/077, BMRC/04/1/21/19/315).‬

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