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Published in:
Archivos de Bronconeumologia

DOI:
[10.1016/j.arbres.2016.11.018](https://doi.org/10.1016/j.arbres.2016.11.018)

Publication date:
2017

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Document Version
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):
Dicker, A. J., & Chalmers, J. D. (2017). Microbial Dysbiosis in Bronchiectasis and Cystic Fibrosis. *Archivos de Bronconeumologia*, 53(9), 471-472. <https://doi.org/10.1016/j.arbres.2016.11.018>

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Editorial: Microbial Dysbiosis in Bronchiectasis and Cystic Fibrosis

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Identification and treatment of bacterial infection is central to our management of bronchiectasis, whether caused by cystic fibrosis or by other underlying disorders.(1) The pathophysiology of these diseases is understood to be a vicious cycle of infection, inflammation and tissue damage which we attempt to break by eradicating or suppressing pathogenic bacteria using inhaled, oral and intravenous antibiotics.(1, 2)

Our understanding of this pathophysiology is being changed, however, by developments in molecular microbiology and genomics. Non-culture based methods of identifying bacteria, viruses and fungi in the lungs of CF and bronchiectasis patients is a rapidly expanding field of research. By utilising high-throughput sequencing platforms to target conserved regions of DNA, such as the bacterial 16S rRNA gene, identification of the bacteria present in sputum, bronchoalveolar lavage (BAL) or upper airway swabs is possible without the need for microbial culture.(3) There is potential to identify potential pathogens more sensitively, to identify non-culturable bacteria, to understand “phenotypes” of disease based on microbiota profiles, and to better understand the impact of treatment on microbes and the host response.

Cystic fibrosis is perhaps the most intensively studied condition with respect to the lung microbiome. Recent data shows that the upper airway microbiome starts to change in CF infants in the first year of life with overgrowth of *Staphylococcus* even in children without antibiotic treatment.(4, 5) As disease progresses, the proteobacteria increase in relative abundance with the emergence of “traditional” CF pathogens such as *Pseudomonas spp.* Longitudinal studies have identified that the lung microbiota is stable over time, at least in the short term, and does not vary significantly during exacerbations.(6) One of the largest studies in CF patients to date (n=269) confirmed patterns of microbiota diversity observed in other smaller-scale studies; dysbiosis (a reduction in microbiota diversity with dominance of one or a few genera) is associated with more severe disease, age and increasing antibiotic use.(7) A subset of genera, namely *Veillonella*, *Burkholderia*, *Prevotella*, *Streptococcus*, *Rothia* and *Actinomyces*, appear to form a core CF microbiota whilst genera like *Pseudomonas* and *Staphylococcus* become more dominant as disease progresses. Very few studies have extensive longitudinal follow up of patients or have data on the impact of therapies such as inhaled antibiotics or CFTR modulators; this will need to be addressed before the utility of microbiota data in clinical settings is fully realised.

The microbiota in bronchiectasis has been less well studied than in CF; small studies have shown that it is diverse and relatively stable over time, with a reduction in diversity identified at exacerbations and also associated with increasing disease severity.(8) Like CF, there are common shared genera such as *Veillonella*, *Streptococcus* and *Prevotella* with dominance of pathogens such as *Pseudomonas* or *Haemophilus* associated with increasing disease severity.(9) Intriguingly, a randomized control trial

(RCT) of erythromycin suggested that long term macrolide therapy, a common treatment strategy, may be associated with an increase in relative abundance of *Pseudomonas spp.*(9) This is important because of the well-known association between *Pseudomonas aeruginosa* infection and poor clinical outcomes.(10) Dominance of *Pseudomonas spp.* by sequencing has also been associated with more exacerbations and increased levels of inflammation such as matrix metalloproteinases.(9, 11)

While there are increasing numbers of bronchiectasis microbiota studies, a significant percentage have arisen from a single RCT in Australia that included only patients with a history of 2 or more exacerbations in the previous year among other exclusion criteria.(9) It has been shown that 52-93% of bronchiectasis patients in real-life are ineligible for RCTs.(12) Larger studies from diverse populations are now needed.

Studies show that individuals microbiota profiles vary significantly from each other; what is normal for one patient during disease stability may not be for another. The key to being able to use microbiota data clinically will be a better understanding of how an individual patients microbiota changes over time, and how this is associated with altered lung inflammatory profiles, clinical phenotypes and clinical outcomes. In both CF and bronchiectasis it appears that this change towards dysbiosis alongside changes in clinical and inflammatory profiles is clinically important and useful to stratify patients. What is now needed is to determine if microbiota profiles can add to existing stratification methods such as the Bronchiectasis Severity Index, by providing additional prediction of exacerbations or treatment response.(13, 14)

A barrier to effective implantation of microbiota data into practice is a lack of agreed technical approaches. Sampling techniques and DNA extraction methods vary greatly. Different regions of the 16S rRNA gene have been sequenced and numerous different sequence analysis pipelines exist. All of these can cause slight variation in the proportions of genera identified. Contamination of samples or laboratory reagents with can cause misleading results if not identified and dealt with, particularly in low biomass samples. These technical and bioinformatic challenges need to be overcome and methods standardised if microbiota data is to become useful in clinical care.

The bacterial microbiota alone will not explain all the phenotypic diversity seen in CF and bronchiectasis patients. Viruses, fungi and mycobacteria also contribute to the lung microbiome in the healthy lung, in CF and bronchiectasis disease stability and exacerbation. Indeed for bronchiectasis no 'virome' or 'mycobiota' studies have been published to date, yet it is acknowledged that mycosis is becoming an increasing problem.(15) In both CF and bronchiectasis, therapeutic and prophylactic use of antibiotics are key parts of the physicians' arsenal, yet whilst the treatments may improve disease symptoms, the effect they have on the fungi, bacteria and viruses inhabiting the

airway is still not known. A better understanding how antibiotic usage in bronchiectasis and CF may contribute towards the development of a dysbiotic microbiome could lead towards better antibiotic stewardship in early disease to slow the development of dysbiosis and drug resistance.

Microbial sequencing technologies are a powerful tool to understand these diseases as never before. Application of novel tools is not, however, an end in itself. The challenge for the pulmonary research community is to now apply this technology to answer clinically important questions and allow microbiome science to have a meaningful impact on patient care.

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