

TITLE: ANALYSIS OF THE INTESTINAL AND RESPIRATORY MICROBIOME IN CHILDREN WITH CYSTIC FIBROSIS: INTERACTION BETWEEN INTESTINAL AND RESPIRATORY SYSTEMS

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ABSTRACT:

Cystic fibrosis (CF) is an autosomal recessive disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene —which encodes the protein CFTR an epithelial chloride and bicarbonate ion channel. Microbial colonization and infections due to impaired airway clearance from thick mucus secretions are the hallmarks of CF lung disease. Similar conditions could contribute to the development of dysbiosis also in the gastrointestinal tract of CF patients. The aim of this study was evaluating the association between respiratory and intestinal microbiome in infants with CF, analysed by sequencing 16S rDNA V3-V4 hypervariable region in the MiSeq platform (Illumina, San Diego, CA) and bioinformatic analysis using R version 3.4.4 and Phyloseq package version 1.22.3. Twenty oropharyngeal and stool samples from 10 patients, homozygotes for *delF508* mutation, were collected in the CF ambulatory. The patients were median age 5,3 years, 55% were female and all have clinically stable lung disease. The sample analysis yields a total of 1,056,505 sequences, which comprised 456 unique Operational Taxonomical Units (OTUs). Among these sequences, 70% of the total number of reads were distributed in 35 main bacterial genera. *Prevotella*, *Streptococcus*, *Rothia*, *Fusobacterium*, *Neisseria*, *Haemophilus* and *Terrahaemophilus* were the dominant genus in respiratory samples, comprising 43% of the total number of reads. *Bacteroides*, *Bifidobacterium*, *Eubacterium*, *Faecalibacterium*, *Escherichia*, *Blautia* and *Lachnospirillum* were the most abundant genera in the intestinal tract, collectively comprising 27% of the total number of reads. We evaluated both the most abundant microbes in the intestinal and respiratory tracts and the inter- and intraindividual variation in the microbial composition and diversity within these two sampling locations and we not found significant difference in α or β -diversity between the oropharyngeal and stool samples. These data suggest that the microbiome of the respiratory and intestinal tract are distinct, despite of there are some bacteria common to both sites. Understanding the complex interactions between the *CFTR* mutations, microbial colonization, and mucosal and systemic immunity is of major importance to apprise new treatment strategies, such as reinstating a healthier microbiome, to improve the affected children's nutritional status and immune competence and to decrease morbidity and mortality in CF.

Keywords: Cystic fibrosis; gut microbiota; airway microbiota, *F508del* mutation; microbiome