Candida albicans in cystic fibrosis: “Opening statements presented, let the trial begin”

Chotirmall, Sanjay Haresh

2015

Chotirmall, S. H. (2016). Candida albicans in cystic fibrosis: “Opening statements presented, let the trial begin” . Pediatric Pulmonology, 51(5), 445-446.

<https://hdl.handle.net/10356/80787>

<https://doi.org/10.1002/ppul.23315>

© 2015 Wiley Periodicals, Inc. This is the author created version of a work that has been peer reviewed and accepted for publication by Pediatric Pulmonology, Wiley Periodicals, Inc. It incorporates referee’ s comments but changes resulting from the publishing process, such as copyediting, structural formatting, may not be reflected in this document. The published version is available at: [<http://dx.doi.org/10.1002/ppul.23315>].

Downloaded on 26 Apr 2023 18:59:38 SGT

**CANDIDA ALBICANS IN CYSTIC FIBROSIS: “OPENING STATEMENTS
PRESENTED, LET THE TRIAL BEGIN”**

Sanjay H. Chotirmall MD PhD

Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

Telephone +65 90614430

Fax +65 63392889

E-mail schotirmall@ntu.edu.sg

Keywords: Candida, Cystic Fibrosis, Colonization, Airway, Trials

Running Head: Candida in Cystic Fibrosis

Financial Disclosures: None

Word Count: 943 words

Cystic fibrosis (CF) is a chronic destructive genetic disease resulting from dysfunction of the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) protein that encodes an apically located chloride ion channel on the cellular epithelial surface. Within the lung, this causes mucociliary impairment and consequently an inability to mobilize secretions. The result is mucus trapping, bacterial colonization, recurrent exacerbations, persistent inflammation, structural bronchiectasis and death predominantly attributed to respiratory failure ^{1,2}. Important advances in understanding disease pathogenesis, particularly on a molecular level, coupled with newer therapeutic approaches have increased the life expectancy for patients with CF (PWCF). Such positive change also brings new and previously unrecognized challenges in disease management. One such challenge remains understanding the role of fungal colonization and infection in PWCF.

Traditionally, CF is associated with bacterial pathogens such as *Staphylococcus aureus* and *Pseudomonas aeruginosa* however an increasing recognition of fungi in the CF airway is described ^{1,2}. While the clinical role for *Aspergillus* species in PWCF has received most attention to date, *Candida* species particularly *C. albicans* are frequently detected in CF sputum. These yeasts are capable of causing localized infection such as oral or genital thrush but also chronic and systemic infection in the post-transplant setting or by infecting implanted vascular access devices ². While this fungal yeast is commonly seen as a commensal in the oropharynx and upper respiratory tract, its role in the lower airway of PWCF remains uncertain.

In this issue of *Pediatric Pulmonology*, Gileles- Hillel and colleagues report findings of an observational longitudinal study from Israel assessing 4,244 sputum samples in n=91 PWCF³. By stratifying patients according to their *Candida* colonization status, they report that patients chronically colonized have worse pulmonary function at study commencement, study completion and also the greatest rates of decline over the study period compared to intermittently and non-colonized cohorts. Likelihood of colonization was also higher in the presence of pancreatic insufficiency, cystic fibrosis related diabetes (CFRD), corticosteroid use and Methicillin-resistant *Staphylococcus aureus* (MRSA). The strongest independent predictors of colonization were FEV1<60% predicted, BMI<20 and interestingly, co-colonization with *Aspergillus* species. This is the second compelling ‘opening statement’ in the case of *Candida* colonization in cystic fibrosis and its potential for direct pathogenesis. The first was a prospective observational study performed with colleagues in Ireland in which we followed n=89 PWCF over an eleven-year period⁴. We discovered that colonization with *C. albicans* was associated with greater longitudinal declines in FEV1, BMI and was also linked to increased hospitalized exacerbation rates. The greatest predictors of colonization in this work were pancreatic insufficiency, co-colonization with *Pseudomonas* species and osteopenia⁴. While the two studies share similarities, there are also inherent important differences to highlight.

First, it should be recognized that these works were carried out in different CF cohorts with the earlier Irish study prospectively conducted and the recent Israeli dataset retrospectively analysed. Contrasting ‘predictors’ for *Candida* colonization were observed between the two studies, however, all cited factors (irrespective of study)

commonly reflect a clinically advanced CF phenotype. Gileles-Hillel *et al* further did not assess lung function preceding *Candida* colonization ³. Coupled with their study design, lack of data on antibiotic use and high occurrence of corticosteroid administration and MRSA frequency, it remains difficult to distinguish associative relationships from potentially causative ones in the setting of *C. albicans* colonization in the CF airway, a similar challenge experienced in our Irish study.

Despite these obvious differences, key similarities subsist between these two works. Both groups detected reduced lung function and associations of *C. albicans* colonization in differing extents to co-colonization with *Pseudomonas* and *Aspergillus* species. This is pivotal in providing a potential biological basis for the investigation of *C. albicans* as an independent pathogen in the CF airway. Certain *Candida* cell wall components induce pro-inflammatory responses and coupled with the known inhibitory effects of *Candida* on host phagocytosis, ability to form drug-resistant biofilms and immunoevasive capability, it is possible that the presence of *Candida* in the CF airway may independently contribute to the deleterious pro-inflammatory state *in-vivo* ¹. Furthermore, the complex inter-species interactions within the CF airway could also have a role. The presence of *Pseudomonas* causes morphological adaptation to *Candida in-vitro* inhibiting its production of virulence factors and biofilm formation. This may be a possible reason that Gileles- Hillel *et al* only discovered statistically significant FEV1 declines in the non-*Pseudomonas* colonized PWCF. Interestingly and in converse fashion, the presence of *Candida* enhances *Pseudomonas* pathogenicity by upregulating its virulence. *Candida's*

relationship to *Aspergillus* co-colonization is less well understood and studies assessing combined colonization states are essential to better understand these relationships.

Overall, when taken together, the two studies are complementary. Whilst neither can discriminate between *Candida* colonization in the CF airway representing a marker of disease severity versus independent pathogen, they together both provide a strong platform to warrant future prospective multicentre randomized controlled therapeutic clinical trials aimed at eliminating *Candida* from the CF airway to test this hypothesis. It is necessary however that such work is carefully designed, for example considering the exclusion of *Pseudomonas* colonized PWCF from such trials to prevent diluting any possible clinical effect of *Candida* elimination from the CF airway. Data should also be serially collected in a longitudinal fashion from the airway and systemically and assessed from a microbiological, inflammatory and immune perspective.

The emergence of the respiratory ‘microbiome’ and more recently the fungal ‘mycobiome’ also needs future consideration ⁵. Both the Irish and Israeli studies discussed, together represent compelling ‘opening statements’ and provide a platform for studying the case of direct *Candida* pathogenesis in PWCF. While the jury listens and the future verdict uncertain at this juncture, the time has certainly come for the ‘trial to begin’.

REFERENCES

1. Chotirmall SH, McElvaney NG. Fungi in the cystic fibrosis lung: bystanders or pathogens? *The international journal of biochemistry & cell biology* 2014;52:161-173.
2. Chotirmall SH, Greene CM, McElvaney NG. *Candida* species in cystic fibrosis: A road less travelled. *Medical mycology* 2010;48 Suppl 1:S114-124.
3. Gileles-Hillel A, Shoseyov D, Polacheck I, Korem M, Kerem E, Cohen-Cymberknoh M. Association of chronic *Candida albicans* respiratory infection with a more severe lung disease in patients with cystic fibrosis. *Pediatr Pulmonol* 2015.
4. Chotirmall SH, O'Donoghue E, Bennett K, Gunaratnam C, O'Neill SJ, McElvaney NG. Sputum *Candida albicans* presages FEV(1) decline and hospital-treated exacerbations in cystic fibrosis. *Chest* 2010;138(5):1186-1195.
5. Nguyen LD, Viscogliosi E, Delhaes L. The lung mycobiome: an emerging field of the human respiratory microbiome. *Frontiers in microbiology* 2015;6:89.