
بسم الله الرحمن الرحيم

PROBIOTIC IN CYSTIC FIBROSIS

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Cystic fibrosis (CF) is a genetic disease caused by mutations in the cystic fibrosis trans-membrane regulator (CFTR) gene, which leads to a deficiency or absence of functional CFTR proteins at the apical membrane of epithelial cells in multiple body systems, including the respiratory and gastrointestinal systems .

This CFTR dysfunction leads to dehydrated and viscous mucus and in the lungs results in inflammation and chronic infections leading to progressive loss of lung function.

This same pathophysiology in the gastrointestinal tract manifests as pancreatic insufficiency, malabsorption, dysmotility, small bowel bacterial overgrowth, functional gastrointestinal symptoms and intestinal obstruction.

Chronic inflammation has been well documented in this fecal calprotectin is the most commonly used biomarker for the measurement of intestinal inflammation.

It is widely acknowledged that the gastrointestinal microbiota play an important role in health and disease and are increasingly recognized as important contributors to immune and metabolic homeostasis .

Disruption to the gut microbiota, dysbiosis, has been associated with a number of inflammatory conditions, including inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) as well as respiratory conditions such as allergic airway inflammation .

A state of dysbiosis has also been demonstrated in the CF gut with an abundance of potentially pathogenic bacteria and a reduction in beneficial bacteria.

Evidence has suggested that these decreases in good gut bacteria can have an impact on:

- Intestinal inflammation
- Digestive issues
- The gut-brain axis
- Growth
- CF-related diabetes
- Lung function decline
- CF liver disease

Modulation of the gut microbiota is increasingly been used as a therapeutic strategy in maintaining health and treating disease through the administration of live bacteria (probiotics).

Probiotics are defined as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host” .

They act in diverse ways to affect the composition or function of the microbiota and by altering host epithelial and immunological responses.

Probiotics have been shown to be effective in gastrointestinal inflammatory conditions such as IBD and IBS as well as in respiratory conditions and allergy . Efficacy has also been shown in the management of antibiotic associated diarrhea (AAD) and Clostridium difficile , suggesting potential for use in CF in whom these conditions have been frequently reported.

In CF, it has been suggested that probiotics may help to restore the intestinal microbial balance altered by the frequent use of antibacterial and antimicrobial therapies for the prevention and treatment of respiratory exacerbations .

Potential mechanisms of action by which probiotics may benefit patients with CF, through their effects on the gut microbiota:

- Changes to gut motility
- Improved intestinal barrier function
- Inhibition of the colonization of pathogenic bacteria
- Improved metabolic processes and modulation of gut and systemic immunity
- They may also exert positive effects on respiratory inflammation and infection through potential crosstalk between the airway and gut microbiota.

Recent systematic reviews showing a decrease in the incidence, duration and severity of respiratory infections with probiotics, albeit in healthy children and adults .

Beneficial effects of probiotic supplementation have also shown a reduction in the number of episodes of allergic rhinitis .

Probiotics may influence respiratory immune responses via a microbial link between the respiratory and gastrointestinal tracts

Inflammatory outcomes:

- Fecal calprotectin (CLP) measured fecal CLP using ELISA techniques showing a significant decrease in CLP with probiotics .The decrease in CLP was shown with both normal and high baseline levels of CLP, although high baseline levels did not always decrease to within normal range post probiotic intervention.

- Other inflammatory markers . Two RCT crossover trials measured IL-8 and TNF-α and one pre–post study measured IL-8 only, all as secondary outcomes, with samples harvested from feces, sputum and plasma. Interleukins IL-1B, IL-10, IL-6 and IL-12 , immunoglobulins (IgG, IgA, IgM) were also measured as secondary outcome measures.

All reported no changes with probiotics except for a minor decrease in eosinophils at three months ($p = 0.03$) post probiotic intake .

Gastrointestinal outcomes :

- Two studies reported the effect of probiotics on measures of **fat absorption** with no significant difference with probiotics compared with placebo .
- Infante reported a significant effect of probiotics on the absorption of sugars (p b 0.05) but not for nitrogen or water .

- Bruzzese et al. reported that abdominal pain decreased in several children after taking probiotics .

- One study assessed the effects of probiotics on the number of gastrointestinal infections finding no difference between probiotic and placebo.

Respiratory outcomes:

❑Number of pulmonary exacerbations (PE) :

Overall studies consistently reported a reduction in the number of PE with probiotics compared with placebo during the intervention period, which was 6 months in all studies which was 1 month. In two studies, a reduction was shown after three and 6 months post intervention, compared with the same time period in the year prior.

❑Number and duration of hospital admissions for PE:

Results were inconclusive for the effects of probiotics on the number of hospital admissions for PE, with no effect shown on duration of hospital stay.

Few studies investigated or were adequately powered to detect the effect of probiotics on FEV1% despite its known association with morbidity and mortality in patients with CF.

Probiotics were shown to significantly decrease the number of pulmonary exacerbations although a small reduction in the number of PE's is clinically important as lung disease is the key determinant of quantity and quality of life in CF with respiratory exacerbations leading to progressive insufficiency and deterioration that ultimately affects long-term prognosis.

Overall, the evidence suggests that probiotics may reduce the number of pulmonary exacerbations and decrease intestinal inflammation; however, the evidence base is limited and studies are of variable quality and risk of bias.