

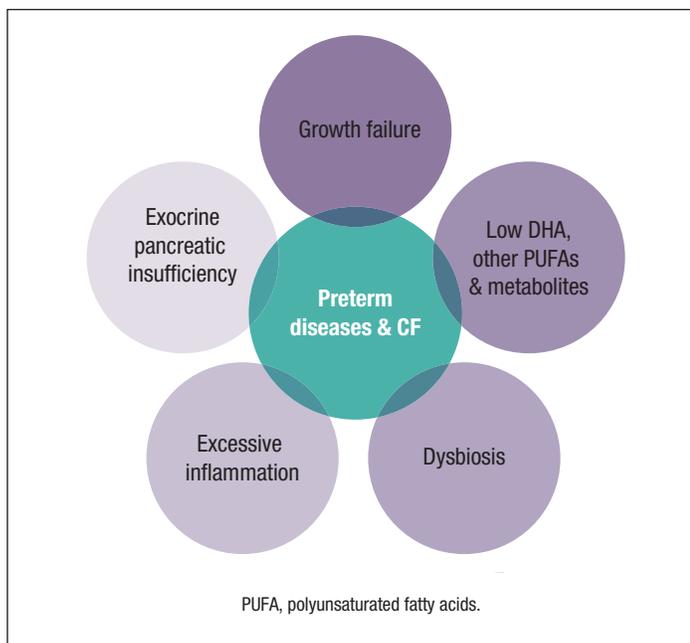
## Breast Milk Fats and Lipids: Expanding Benefits to Fragile Infant Populations

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The benefits of breast milk are well established for preterm and healthy term infants, yet much less is known regarding the impact of breast milk and its associated lipids on the treatment of diseases in infant and pediatric populations. Diseases in infancy, such as cystic fibrosis (CF), often have many similarities with diseases of prematurity (**Figure 1**). For example, both prematurity and CF are associated with altered fatty acid levels and low levels of docosahexaenoic acid (DHA), which may be responsive to breast milk therapy. Due to its parallels to preterm infant physiology and pathophysiology, CF may represent an ideal infant population to study the role of human milk and/or cream as potential therapeutics.

**Figure 1. Similarities between preterm infants and infants with CF.**



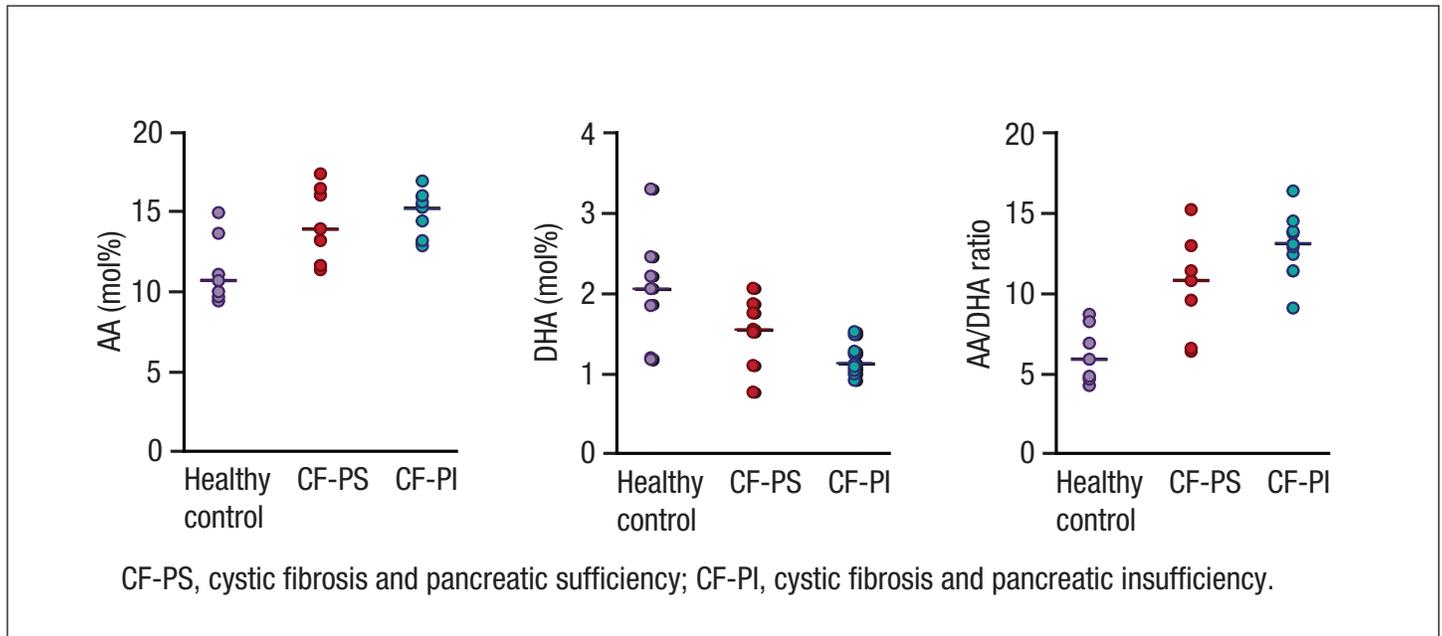
CF is a genetic disease caused by mutations in the gene coding for the CF transmembrane conductance regulator (CFTR) chloride channel.<sup>1</sup> CFTR is localized to the apical membrane of epithelial cells and plays an important role in regulating fluid secretion. Disruptions in CFTR-mediated chloride transport results

in abnormally viscous secretions and obstruction of epithelial-lined tubes throughout the body. Obstructions in the lungs can lead to infection and inflammation, resulting in the development of lung disease.<sup>2</sup> Furthermore, malnutrition in CF patients (related to exocrine pancreatic insufficiency, intestinal defects, and low levels of insulin-like growth factor-1 [IGF-1]) is also linked to lung disease.<sup>3</sup>

Findings from studies in animal models of CF suggest loss of CFTR function alters cellular fatty acid metabolism. The lungs, pancreas, and ileum of *cftr(-/-)* mice were shown to have increased levels of membrane-bound arachidonic acid (AA), an activator of mucous secretions and inflammation, and decreased levels of membrane-bound DHA.<sup>4</sup> Oral administration of DHA to *cftr(-/-)* mice corrected the lipid imbalance and reversed the pathology in the pancreas and ileum. In *cftr(-/-)* mice exposed to aerosolized *Pseudomonas aeruginosa* lipopolysaccharide, DHA administration reduced neutrophil and eicosanoid concentrations in the lung, suggesting the membrane lipid imbalance observed in *cftr(-/-)* mice may play a role in the immune response to lung infection.<sup>5</sup> Furthermore, DHA has been shown to prevent bile duct injury in *cftr(-/-)* mice with colitis (induced with dextran sodium sulfate) through increases in peroxisome proliferator activated receptor alpha (PPAR $\alpha$ ), a transcription factor involved in lipid metabolism and regulation of inflammatory responses.<sup>6</sup>

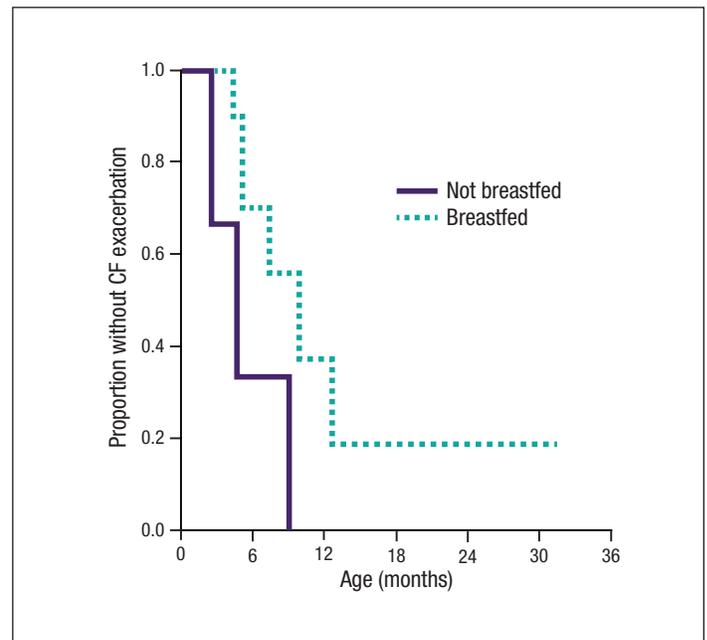
Alterations in fatty acid metabolism are also seen in humans with CF. Nasal mucosal biopsies from patients with CF showed higher levels of AA and lower levels of DHA compared with healthy controls (**Figure 2**).<sup>7</sup> A small pilot study in patients with primary sclerosing cholangitis (PSC), a bile duct disease linked to CFTR dysfunction, found that DHA supplementation over 52 weeks was effective in reducing levels of serum alkaline phosphatase, a marker for disease progression.<sup>8</sup> Serum DHA levels significantly increased from baseline, while serum AA levels significantly decreased, suggesting DHA supplementation could correct CFTR-related fatty acid abnormalities in patients with PSC.

**Figure 2. Altered fatty acid levels in CF patients.<sup>7</sup>**



Human milk could be used to help correct the underlying pathophysiologic processes associated with CF by providing nutrition for growth, supplementation of fatty acids (eg, DHA), modulation of the gut microbiome, and other anti-inflammatory mediators (eg, human milk oligosaccharides). A survey of CF patients (3,200 questionnaires sent to 30 CF centers) found exclusive breastfeeding for  $\geq 6$  months was associated with a significant decrease in the number of intravenous antibiotic courses and a trend toward delayed onset of first infection, demonstrating that breastfeeding is safe and likely beneficial in infants with CF.<sup>9</sup> Similar findings were reported in a retrospective study of children with CF; prolonged breastfeeding was associated with improved lung function and a lower number of infections during the first 3 years of life.<sup>10</sup> A prospective cohort study from the Wisconsin Routine Newborn CF Screening Program (N = 103) showed that exclusively breastfed infants with CF had fewer *Pseudomonas aeruginosa* infections during the first 2 years of life.<sup>11</sup> Lastly, findings from a prospective longitudinal cohort study in infants and children with CF showed any breast milk exposure was an important determinant of microbial diversity in the respiratory tract.<sup>12</sup> A trend toward prolonged time to first CF exacerbation (Figure 3) and *Pseudomonas aeruginosa* colonization was seen among breastfed infants.

**Figure 3. Time to first CF exacerbation.<sup>12</sup>**



Taken together, the data from these studies in infants and children suggest that human milk and/or its selective components may have a major health impact in infants with CF and could affect long-term health outcomes. Given the parallels between prematurity and infants with CF, this provides an opportunity for CF researchers and neonatologists to develop fortification strategies and identify unique human milk components to optimize nutrition and growth and to address the abnormal immune and organogenesis pathways leading to disease.

## References

1. Cutting GR. Cystic fibrosis genetics: from molecular understanding to clinical application. *Nat Rev Genet.* 2015;16(1):45-56.
2. Stoltz DA, et al. Cystic fibrosis pigs develop lung disease and exhibit defective bacterial eradication at birth. *Sci Transl Med.* 2010;2(29):29ra31.
3. Yen EH, et al. Better nutritional status in early childhood is associated with improved clinical outcomes and survival in patients with cystic fibrosis. *J Pediatr.* 2013;162(3):530-535.e1.
4. Freedman SD, et al. A membrane lipid imbalance plays a role in the phenotypic expression of cystic fibrosis in *cftr(-/-)* mice. *Proc Natl Acad Sci U S A.* 1999;96(24):13995-14000.
5. Freedman SD, et al. Characterization of LPS-induced lung inflammation in *cftr(-/-)* mice and the effect of docosahexaenoic acid. *J Appl Physiol* (1985). 2002;92(5):2169-2176.
6. Pall H, et al. Decreased peroxisome proliferator activated receptor alpha is associated with bile duct injury in cystic fibrosis transmembrane conductance regulator-/- mice. *J Pediatr Gastroenterol Nutr.* 2006;42(3):275-281.
7. Freedman SD, et al. Association of cystic fibrosis with abnormalities in fatty acid metabolism. *N Engl J Med.* 2004;350(6):560-569.
8. Martin CR, et al. The safety and efficacy of oral docosahexaenoic acid supplementation for the treatment of primary sclerosing cholangitis - a pilot study. *Aliment Pharmacol Ther.* 2012;35(2):255-265.
9. Parker EM, et al. Survey of breast-feeding practices and outcomes in the cystic fibrosis population. *Pediatr Pulmonol.* 2004;37(4):362-367.
10. Colombo C, et al. Benefits of breastfeeding in cystic fibrosis: a single-centre follow-up survey. *Acta Paediatr.* 2007;96(8):1228-1232.
11. Jadin SA, et al. Growth and pulmonary outcomes during the first 2 y of life of breastfed and formula-fed infants diagnosed with cystic fibrosis through the Wisconsin Routine Newborn Screening Program. *Am J Clin Nutr.* 2011;93(5):1038-1047.
12. Hoen AG, et al. Associations between gut microbial colonization in early life and respiratory outcomes in cystic fibrosis. *J Pediatr.* 2015;167(1):138-47.e1-3.