

# Cystic Fibrosis: Therapeutic Options For Co-management.

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## Abstract:

Cystic fibrosis (CF) is a cruel and deadly disease affecting the respiratory system, digestive system, endocrine system, and reproductive system. CF is a disease of greatly varied symptomatology due to the many possible mutations contributing to genotype and phenotype. This creates a disease complex with a wide range of disorders that can ultimately include chronic obstructive pulmonary disease, CF-associated liver fibrosis, diabetes mellitus, cholelithiasis, and arthritis. The primary destructive component, however, is seen in the lungs, resulting in the uncertain life span associated with this disease. Controlling bacterial infection and managing the status of macro- and micronutrients remain a constant challenge. Due to the severity of this recessive disorder, conventional medical treatment is mandatory. However, many alternative medical options, such as coenzyme Q10, oligomeric proanthocyanidins, antioxidants, and amino acid therapies have proven to be significant contributors to the treatment of one of the ultimate co-management diseases of our time.

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## Introduction

Cystic fibrosis (CF) is the most common lethal autosomal recessive disease found in the Caucasian population, with a frequency of approximately one in 2,500 births.<sup>1,2</sup> There are at least 500 different genetic mutations associated with the disease, thus making homozygous and heterozygous screening procedures difficult.<sup>3</sup> However, approximately 70% of the mutations are found to be delta F508, making it the most common CF mutation.<sup>4</sup>

Delta F508 mutation is consistently associated with a single haplotype “B” which seems to support a “selective advantage” hypothesis.<sup>5</sup> The possible selective advantage for the carriers of CF mutations (heterozygote advantage) could be a defense against the profuse diarrhea and fluid loss seen in cholera.<sup>6,7</sup> Other selective advantage ideas exist as well. The hypothesis of increased resistance to human strain *Mycobacterium tuberculosis*, increased resistance to influenza, and protection against bronchial asthma in childhood and early adult life all present interesting possibilities.<sup>8-10</sup>

The primary CF defect is expressed as altered ion transport via the cystic fibrosis transmembrane conductance regulator (CFTR), which is the protein regulating cyclic-AMP-mediated chloride conductance at the apical membranes of secretory epithelia.<sup>10</sup> Specifically, the normal release of intracellular chloride into extracellular fluids fails to respond to normal cAMP elevation. This impaired release of chloride results in the dehydration of surrounding respiratory and intestinal mucosal linings and impaired sodium reabsorption of the sudoriferous glands. This mucosal dehydration, coupled with inflammatory and infective byproducts, creates a thick

**Table 1.** Other Causes of Elevated QPIT

- Adrenal insufficiency
- Hypothyroidism
- Hypopituitarism
- Hypoparathyroidism (familial)
- Mucopolysaccharidosis
- Nephrogenic diabetes insipidus
- Glycogen storage disease type I
- Malnutrition
- Fucosidosis
- Ectodermal dysplasia

and tenacious mucus that clogs and damages airways. Diagnostic criteria includes a quantitative pilocarpine iontophoresis test (QPIT) for sweat chloride of 60 mEq/L or greater.<sup>11</sup> There are some rare differential diagnostic causes of an elevated QPIT which may be considered in the early stages of a CF rule-out, particularly in infants (see Table 1).

### The Lungs in CF

The most pressing and compelling clinical presentations of CF are due to chronic lung inflammation. Airway epithelial destruction, bronchiectasis, and chronic obstructive pulmonary disease (COPD) are inevitable, due to a constant respiratory burden of inflammatory oxidant production.<sup>12</sup> This release of toxic oxygen species (TOS) and proteolytic enzymes from bacterial and inflammatory cells is of prime therapeutic concern. Airway recruitment of neutrophils and pulmonary macrophages also generates lung-damaging metabolites and leukotriene B<sub>4</sub> (LTB<sub>4</sub>). LTB<sub>4</sub> has been identified as a strong local mediator in the inflammatory process by stimulating the movement of massive numbers of neutrophils into the airways. An arachidonic acid metabolite, LTB<sub>4</sub> is a powerful agent of chemotaxis when instilled experimentally into the endotracheal tissue of humans.<sup>13</sup> Various levels of LTB<sub>4</sub> have been identified in the sputum of CF-affected individuals.<sup>14</sup>

Research has shown that dietary supplementation with omega-3 fatty acids increases the cell membrane phospholipid content of eicosapentaenoic acid (EPA). The suggested benefits of this dietary protocol are decreased LTB<sub>4</sub> release and increased

leukotriene B<sub>5</sub> (LTB<sub>5</sub>) release by neutrophils. LTB<sub>5</sub>, an EPA metabolite, displays minimal leukocyte chemotaxis in comparison

to LTB<sub>4</sub>.<sup>15-17</sup> A preliminary, placebo-controlled study of EPA supplementation in CF (2.7 g daily for 6 weeks) revealed a significant decrease in sputum volume ( $p = 0.015$ ), increased forced expiratory volume in one second ( $p = 0.006$ ) and significantly increased vital capacity ( $p = 0.011$ ).<sup>18</sup> One potential barrier to this approach would be malabsorption of EPA.

In addition to dehydration creating a thick, inspissated mucus, glycoproteins and DNA fragments from spent granulocytes will also increase mucus viscosity (see Figure 1). Airway destruction and viscous non-clearing

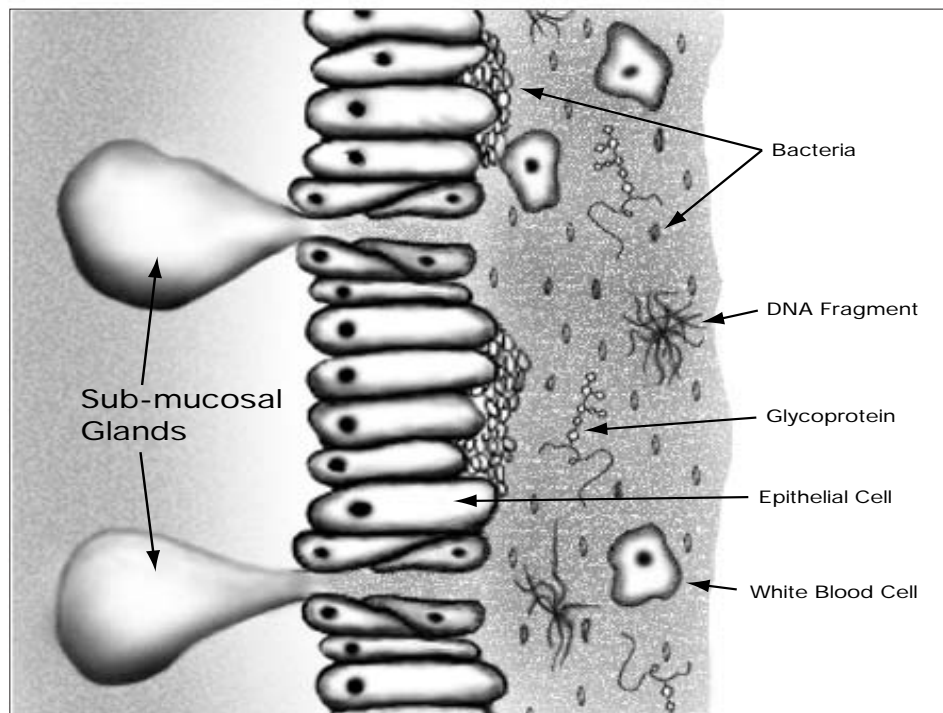
**Table 2.** Respiratory and Cardiac Clinical Presentations of Cystic Fibrosis

- Atelectasis
- Bronchitis, bronchopneumonia, bronchiectasis, lung abscess
- Congestive Heart Failure
- Cor Pulmonale
- Hemoptysis
- Pneumothorax
- Pulmonary hypertension
- Sinusitis, nasal polyps
- Respiratory failure

secretions account for much of the fatal progressions of the disease, as shown in Table 2. Ninety percent of CF mortality is due to respiratory failure.<sup>19</sup>

Contributing to the overall chronic state of this disease is the *Pseudomonas aeruginosa* bacteria, which is eventually colonized by virtually every CF patient. This

**Figure 1.** The Cystic Fibrosis-Affected Lung



• Adapted From Scientific American December 1995

endobronchial infection is the major cause of the chronic obstructive component found in CF,<sup>20,21</sup> and *P. aeruginosa* has come to dominate the microbiological landscape of this disease since the successful development of anti-staphylococcal antibiotics.<sup>22</sup> Once *P. aeruginosa* is colonized, it remains present in the CF sputum in densities of at least 100K bacteria per gram of sputum.<sup>23</sup> The possibility also exists that long-term anti-staphylococcal therapy has contributed to the early onset of *P. aeruginosa*.<sup>24</sup>

Localized factors are thought to be responsible for the initial and ongoing infective pattern seen in CF. For example, *P. aeruginosa* is confined to small and medium airway surfaces, sparing terminal and respiratory bronchioles and alveolar spaces. Therefore, the organism rarely, if ever, crosses the alveolar-capillary membrane to cause bacteremia. Signs of a systemic immune defect are not normally observed. This organism is so characteristic of CF that any non-hospitalized patient testing positive for *P. aeruginosa* should always have CF included in a differential diagnosis. A significant finding is that the lung histology

of CF infants is normal at birth, yet, while the infant may be asymptomatic, infective bronchial changes and increased granulocyte activity ensue. There is also recent evidence in infants as young as four weeks that the airway inflammatory response precedes any bacterial infection.<sup>25</sup> *P. aeruginosa* is extremely virulent, due to this organism's ability to: (1) produce proteases that interfere with phagocytic diapedesis and chemotaxis, (2) synthesize a mucoid

shield (exopolysaccharide coat) which protects the organism against host defenses, and (3) launch a timely resistance to antibiotics.<sup>20</sup> The organism is also quite prevalent and primarily found in a wet environment. *P. aeruginosa* has been recovered from medical equipment utilizing water, including sinks, drains, humidifiers, swimming pools, and whirlpools.<sup>26</sup>

With a recent and unprecedented increase in the success of diagnosis and treatment modalities for the pulmonary component of cystic fibrosis, the estimated median survival age for those born in the 1990's is now 40 years.<sup>27</sup> Pancreatic enzymes, antibiotic advances, nutritional supplementation, and attention to diet have contributed to this overall increase in survival frequency. Improved nutritional status, in particular, has made a consistent positive difference in the main concern of the disease, pulmonary health. The last two decades have shown that optimal nutrition is paramount to lung health and the subsequent lengthening of the life span of infants, children and young adults with CF.<sup>28,29</sup> The irony of this success is that with more CF

**Table 3.** Gastrointestinal Clinical Presentations of Cystic Fibrosis

A. Intestinal	B. Hepatobiliary	C. Pancreatic
Meconium ileus	Loss of bile salts	Pancreatic insufficiency, causing nutrient deficits and diminished growth
Meconium ileus equivalent (distal intestinal obstructive syndrome)	Gall bladder atrophy	Steatorrhea
Volvulus	Cholelithiasis	Diabetes mellitus
Rectal prolapse	Focal or multilobular biliary cirrhosis	Recurrent pancreatitis
Intussusception	Portal hypertension	Tumors
Ileal atresia	Esophageal varices	
Fecal impaction	Hemorrhoids	
Tumors	Hypersplenism	
	Tumors	

patients reaching adulthood, the hepatobiliary and pancreatic components of the disease will have more time to become problematic. With this increasing age of survival and subsequent clinical presentation, the challenge to the patient, family members, and medical team is to balance and maintain more biosystemic variables. In an effort to constantly strive for quality of life in an uncertain life span, we must manage this ruthless and complicated disease which effects a multitude of the body's systems, and usually results in a premature death.

### The Digestive System in CF

The gastrointestinal component of CF creates an elevated risk of fat-soluble vitamin and other micronutrient deficiencies, and protein-calorie malnutrition.<sup>30-33</sup> CF-related malnutrition is actually a triad of reduced energy intake, increased energy loss, and increased energy expenditures. Decreased fat catabolism from hepatobiliary disease contributes to reduced energy intake.<sup>31,33</sup> Fat malabsorption from pancreatic insufficiency contributes to increased energy loss,<sup>34</sup> and results in large, frequent, bulky, malodorous stools. Chronic pulmonary infections, febrile states, aerosolized bronchodilator medications, and an increase in overall respiratory effort contribute to increased energy expenditures.<sup>35</sup> The various gastrointestinal complications that can arise are found in Table 3.

### The Liver and Gallbladder in CF

The dominant features of hepatobiliary involvement in CF are fatty liver, cirrhosis, and gallbladder anomalies. Diagnosis of the precise liver component in CF can be difficult, since the CFTR is mainly expressed in the epithelial cells of the bile duct.<sup>36</sup> CF can be seen as one of the few inherited diseases involving the liver in which the genetic flaw is expressed in the bile duct epithelium instead of hepatocytes. To further the diagnostic mystery, the classic hypoalbuminemia seen in hepatic disease could be due to poor intake or catabolic malnutrition. A palpable liver edge could be due to the pulmonary hyperinflation component of the disease as well. Hepatobiliary disease, cirrhosis, and esophageal varices are more commonly diagnosed in adults with CF than they are in children.<sup>36</sup> When liver damage is suspected, serum albumin, serum bile acids, prothrombin time, partial thromboplastin time, direct bilirubin, and liver enzymes should be obtained. Serum GGT may be the sole elevated liver enzyme indicating liver injury.<sup>37,38</sup> The prevalence of a hepatobiliary component in CF patients increases with age; current estimates are as high as 15%, with the mean age of clinical presentation being 9.8 years.<sup>36</sup> Liver disease in CF can also be the prevailing feature of the disorder.<sup>37</sup> Many researchers have looked for various CF gene mutations that show increased frequency of liver disease.

**Table 4.** Reproductive Clinical Presentations of Cystic Fibrosis

- A. Male sterility (98% of males)
  - Vas deferens is absent or defective
  - Epididymis is absent or defective
  - Seminal vesicles are absent or defective
- B. Female decreased fertility
  - Fallopian tubes have increased viscosity of mucus
  - Vagina has increased viscosity of secretions

Even though the genotype frequencies between those with and without liver disease are not significantly different, some studies have shown a clinical risk relationship.<sup>39-41</sup> Liver disease occurs mainly in CF patients with pancreatic insufficiency, and those with a history of meconium ileus or meconium ileus equivalent (MIE) are four times as likely to develop liver complications.<sup>39</sup>

### The Pancreas in CF

Pancreatic insufficiency or pancreatic failure is seen in approximately 85% of the patients with CF.<sup>32,33</sup> The delta F508 mutation has been found to have a close association with pancreatic health. Most patients with this common genotype have pancreatic insufficiency, while most of the less common genotypes are pancreatic sufficient. However, there are some exceptions. Osborne and co-workers have classified mutation Ni 303K, which accounts for only 1.5% of the CF chromosomes, as a severe mutation with respect to the pancreas.<sup>42,43</sup> Although only about 2% pancreatic enzyme secretion is needed to prevent steatorrhea,<sup>44</sup> it is important to note that pancreatic sufficiency is in reference to fat absorption and digestion only (exocrine). A CF patient might not exhibit steatorrhea, yet other forms of pancreatic dysfunction (endocrine) can be present.<sup>32,33</sup> For example, cystic fibrosis-related diabetes is seen in about 20% of CF patients that reach adulthood.<sup>45</sup>

The many aspects of this complicated disease reach a multitude of body tissues.

Epithelial linings, being quite prevalent throughout the body, are primary targets. Reproductive, bone, and long-term complications are listed in Tables 4 and 5.

### Tobramycin

The primary treatment goal is to optimize lung health by controlling bacterial infection (*P. aeruginosa*) and mobilizing viscous secretions. The most successful anti-pseudomonal treatment has been tobramycin, which is a more effective aminoglycoside than gentamicin by approximately 50% *in vitro*. The intravenous (IV) route necessary for tobramycin therapy contributes to the drug's nephrotoxic and ototoxic potential, and requires routine monitoring of serum levels.<sup>21</sup> Aerosolized tobramycin has proven to be promising for the treatment of *P. aeruginosa* infections in more stable patients and does not appear to spawn organism resistance.<sup>46</sup> Aerosol routes deliver more medication with less toxicity and provide greater lung access.<sup>47</sup> Aerosol routes are also easier for patient and family because treatments can be taken at home in lieu of in-patient IV administration.

### DNase

Neutrophilic death causes the release of oxidants, proteases, actin, and DNA fragments. Both actin and DNA fragments contribute to the viscosity and tenaciousness of CF mucus. Aerosolized DNase I, a drug capable of cleaving DNA strands, has been shown to decrease CF mucus viscosity both *in vitro* and *in vivo*. One recommended dosage is 2.5 mg q.d. or b.i.d. This approach can mobilize secretions in some patients.<sup>47</sup>

### UDCA

Patients with meconium ileus history or MIE might show improvement with preventative treatment using ursodeoxycholic acid (UDCA). This is the dominant bile acid found in polar bear liver, and accounts for a

small portion of the bile acids in humans. UDCA is a competitive inhibitor for the absorption of cholic acid in the terminal ileum. Hoffman and Leuschner have based the therapeutic rationale of UDCA on choleresis (increased bile secretion). UDCA is a hydrophilic bile acid which can decrease bile viscosity for improved bile flow. UDCA is also thought to create hepatocyte resistance to the cytotoxins of hydrophobic bile acids.<sup>48,49</sup>

### Bio-repair

Gene therapy exhibits a great deal of promise for a possible cure for CF. There is clear evidence that normal CFTR gene transfer is possible to the epithelium of CF airways. Gene therapy has managed to correct the CFTR defect in human bile duct cells as well. Via adenoviral vector gene complementation, the induction of a cAMP halide efflux persisted for up to 31 days, keeping the chloride channels patent.<sup>50</sup> The high mitotic rate of the labile cells found in lung airways and in the gastrointestinal tract is one of the hurdles that must be overcome to ensure long-term expression of the transferred gene.

### Pancreatic enzymes

The purpose of pancreatic enzyme replacement therapy (PERT) is to correct steatorrhea, reduce the size and frequency of stools, and relieve abdominal pain. Enhanced and increased absorption of fats and proteins for energy and growth are also a primary goal. The dosage of PERT is titrated to decrease the above mentioned symptoms, with necessary caution to avoid overuse or high-potency enzymes. Reports of colonic strictures in CF patients taking high protease concentrations are of great concern,<sup>51</sup> since the progressive narrowing of the colonic lumen is irreversible.<sup>52</sup> Occasionally CF patients complain of perianal itching. This discomfort occurs when pancreatic enzymes remain inactive and therefore unabsorbed until they reach the

descending colon, sigmoid colon, and rectum. Due to an increase in gastric secretions, bile acid abnormalities, and decreased pancreatic bicarbonate, the duodenal pH is lower than the norm in CF patients, and therefore H<sub>2</sub> receptor blockers such as ranitidine can improve absorption of pancreatin.<sup>53</sup>

### N-acetylcysteine

N-acetylcysteine (NAC) is a cysteine amino acid derivative which is capable of cleaving the disulfide bonds found in mucus, and can be aerosolized or taken orally.<sup>54</sup> In one cross-over study, 52 CF patients positive for *P. aeruginosa* were administered 200mg of NAC orally three times per day for patients <30Kg and 400mg of NAC twice daily for

**Table 5.** Osseous and Miscellaneous Clinical Complications of Cystic Fibrosis

A. Osseous
Demineralization
Osteoporosis
Osteopenia
Hypertrophic osteoarthropathy
B. Miscellaneous Complications
Salt depletion (especially in young children)
Heat stroke
Hypertrophy of apocrine glands
Hypertrophy of salivary glands
Retinal hemorrhage
Psychosocial issues

those >30Kg. Thirty-one patients completed the three-month study, and patients with peak expiratory flow rates (PEFR) of < 70% showed significant improvements in PEFR and forced vital capacity over their predicted values.<sup>55</sup>

NAC has valuable hepatotoxicity protection as a precursor in glutathione synthesis.<sup>56</sup> Stagnaro et al suggest that NAC provides lymphocytic protection against toxic oxygen species. Utilizing ten patients with chronic lung disease and ten gender/age-matched controls, 600 mg of oral NAC was given daily for ten days. A parallel *in vitro* control and study trial exposed lymphocytes to TOS prior to being instilled with NAC. Results showed a decrease in lymphocyte activity by 50% and 65% in the control and study groups, respectively. This demise was reversed by the addition of NAC to the culture medium. The author's summation is that NAC may be able to protect lymphocytes from the destructive forces of TOS, both *in vivo* and *in vitro*.<sup>57</sup> A suggested daily NAC dosage for the adult with CF is 500 mg two to three times per day. This therapeutic effort could decrease hepatotoxin formation and mucous viscosity in CF.

### **Glutathione**

Bacteriocidal oxidants can overload the endobronchial terrain and feed the fires of inflammation. This staggering burden increases the oxidative sensitivity of the CF lung, resulting in further injury of lung parenchyma. Data supports evidence of a decrease in the antioxidant tri-peptide glutathione.<sup>12</sup> In the reduced form, glutathione protects erythrocytes by detoxifying hydrogen peroxide. In the future, an aerosolized glutathione might prove to be a significant antioxidant therapy.

### **Lecithin**

Lecithin (phosphatidylcholine) catabolizes the esterification of cholesterol, which increases cholesterol solubility.<sup>58</sup> The importance of as-close-to-normal bile flow in CF merits emphasis. Bile acids are necessary for normal intestinal absorption of dietary fats, as well as intestinal water and electrolyte transport. They are also the driving force

behind the hepatic flow of bile. Because lecithin emulsifies fats, it also plays an important role in fat absorption. A dose of 1200 mg every day or every other day can be used in the adult patient with CF.

### **Taurine**

The formation of steroidal compounds from cholesterol, which takes place solely in the liver, is dependent on bile acid metabolism. Hepatocytes form a 2-4 gram bile acid pool that has approximately ten enterohepatic cycles per day. Bile acids have a detergent-like function that forms micelles and decreases constituent surface tensions. In this way, bile insolubles and intestinal insolubles are kept in solution to facilitate transport and absorption. Taurine is an amino acid that is one of the main conjugates for bile acids prior to their release into the bile. The terminal ileum is the main absorption site for the enterohepatic recycling of approximately 80% of these acids. Most CF patients suffer from malabsorption, where much of the insult is in the ileum. Since 90% of nutrient absorption takes place in the small intestine, bile acids are therefore malabsorbed as well. Taurine has been shown to decrease fecal fatty acid and sterol excretion. Taurine supplementation can also decrease the severity of steatorrhea associated with many CF cases.<sup>59,60</sup> In one double-blind crossover study, thirteen CF children with steatorrhea of at least 13 grams per day were treated with a taurine dose of 30 mg/kg/day. The study continued for two consecutive four-month durations and involved placebo contrasts as well. Ninety-two percent of the CF children showed decreased fecal fatty acid and sterol excretion while taking taurine.<sup>59</sup> In CF patients with a high degree of steatorrhea, bile acid absorption was increased with taurine supplementation, suggesting a possible role for taurine in treating malabsorption.<sup>60</sup>

### Coenzyme Q10 (CoQ10, ubiquinone)

Coenzyme Q10 is a lipid-soluble quinone present in every cell in the body. During intracellular respiration, CoQ10 collects reducing equivalents and is then converted to the reduced form, Coenzyme QH2. The immune-enhancing effects of supplemental CoQ10 include an increase in granulocyte proliferation, and an increase in overall macrophage activity. The most interesting effects are a prolonged survival of mice infected with *P. aeruginosa*.<sup>61,62</sup> This might be connected with the ability of CoQ10 to increase antioxidant protection in cell membranes, as well as to function at Golgi and plasma cell membrane sites in secretion-related membrane flow and growth control.<sup>63</sup> Via its antioxidant activity, CoQ10 also assists in recycling and sparing vitamin E.<sup>64</sup> Thus, in humans with CF, CoQ10 could prove to be an adjunct in the demanding treatment of *P. aeruginosa* infections and in better control of the inflammatory immune response. Suggested dosage of CoQ10 is 60 mg to 100 mg per day.<sup>65</sup>

### Coleus Forskolii

Forskolin is a labdane diterpene and the active constituent obtained from the *Coleus forskolii* plant. It is a powerful stimulator of cAMP.<sup>66</sup> This diterpene also has the ability to stimulate parietal cell HCl, pepsin, and pancreatic enzyme secretion,<sup>67</sup> which, if used judiciously, is of benefit in CF macronutrient absorption. Forskolin also inhibits platelet aggregation and inflammation by antagonizing the action of platelet-activating-factor. Forskolin derivatives are powerful bronchodilators and have been shown to inhibit bronchoconstriction induced by inhaled leukotriene D4.<sup>68</sup> This could have tremendous value in creating a calming effect on the immune and inflammatory chaos seen in CF lungs.

### Oligomeric Proanthocyanidins (OPCs, pycnogenols)

These oligomeric flavonoids prevent the formation and release of chemical mediators such as leukotrienes, histamine, prostaglandins, and serine proteases.<sup>69</sup> Proanthocyanidins also inhibit the activities of the oxy-radical enzyme xanthine oxidase, are free radical scavengers, and decrease proteolytic enzymes that are disruptive and damaging to collagen proteins.<sup>70</sup> The value in such an application is similar to that of omega-3 fatty acids; in helping to decrease the production of inflammatory oxidants, and thereby reducing some of the subsequent lung damage.<sup>12</sup>

### Fat soluble vitamins

It is apparent that oxidative stress plays a role in the pathogenesis of CF.<sup>71-73</sup> Chronic lung inflammation, combined with antioxidant deficiencies due to malabsorption, create an ongoing oxidant-antioxidant imbalance favoring oxidation. Antioxidant protection appears to be an extremely important part of CF management. Vitamin E deficiency in CF is associated with impaired resistance of low-density lipoprotein (LDL) oxidative stress, which is fully normalized with vitamin E supplementation.<sup>74,75</sup> Due to fat malabsorption which is common in CF patients, water-soluble emulsified forms of vitamins A and E are better absorbed than fat soluble forms.<sup>76-78</sup> Peters and Kelly have shown that even well-nourished CF children have subnormal erythrocyte vitamin E concentrations if supplements are not used on a regular basis. Therefore, a good diet alone will not ensure adequate vitamin E levels to combat the oxidative stress seen in CF.<sup>79</sup> A recommended dosage for vitamin E is 200-500 I.U. per day for the adult with CF. A recommended adult daily intake for vitamin A is 8000 I.U. The benefits of beta-carotene supplementation in CF have been studied and documented as well. LDL oxidation resistance increases



and lipid peroxide formation decreases with beta-carotene enrichment, and an overall excess lipid peroxidation secondary to beta-carotene deficiency can be curtailed with proper supplementation.<sup>80</sup> Oral beta-carotene of 850 I.U./kg/day is effective for beta-carotene normalization in CF patients.<sup>81</sup> Vitamin K is occasionally required in CF. In the presence of liver disease or during prolonged antibiotic therapy which is disruptive to normal colonic flora, a 5 mg dose of vitamin K1 should be given bi-weekly.<sup>82</sup>

### **Carnitine**

For long-chain fatty acids (14 to 24 carbon atoms) to be oxidized and used as cellular fuel, they must enter the mitochondria, where beta oxidation occurs. The activation and entry of long-chain fatty acids into the mitochondria from the extra-mitochondrial cytoplasm requires the presence of carnitine. Carnitine is an important intracellular carrier molecule for the transfer of the acyl group from fatty acyl-CoA to acylcarnitine. This process is complete with the transfer of the acyl group from acylcarnitine to intra-mitochondrial CoA, which takes place on the inner surface of the inner mitochondrial membrane. Carnitine prevents toxic accumulation of long-chain fatty acids in the cytoplasm and of acyl CoA in the mitochondria.

Depressed levels of acylcarnitine have been noted in the cord blood of CF infants, suggesting a disturbance in carnitine regulation coupled with malabsorption.<sup>83</sup> Fat malabsorption, a common CF-related malady, might benefit from a carnitine-rich diet and carnitine supplements.

### **Medium-chain triglycerides**

Medium-chain fatty acids, from supplemental medium chain triglycerides (MCTs), do not require carnitine for entrance into the mitochondria, and are transported directly to the liver via the portal circulation.

For any CF child showing failure to thrive due to malabsorption, the long-term use of dietary MCTs is fully justified. Results from long-term MCT use include decreased steatorrhea and clinical improvements such as weight gain and increased serum albumin levels.<sup>84</sup>

### **Exercise**

The role of mild to moderate exercise is also of great importance as a CF treatment modality. Exercise activity can improve cardiorespiratory conditioning and self image, and can increase appetite.

### **Conclusion**

The favorable progress of gene therapy, nutritional treatments, and antibiotic administration for CF is expected to extend the life-span of these patients. Unfortunately, the pervasiveness of hepatobiliary, pancreatic, and intestinal complications can be expected to rise as a result of this progress. CF is a complex, multisystem disease requiring co-management by health care practitioners, and the importance of a knowledgeable and cooperative health care team cannot be overemphasized. The relatively high incidence of this disorder (1 in 2,500 births) requires increased awareness among physicians. Increased survival rates, subsequent complications, and varied mutations which could leave some patients undiagnosed until adulthood, all underscore the need for ongoing research and education. Because of the multiple and varied disorders seen in the CF patient, it is imperative that practitioners of medical disciplines work together, utilizing not only conservative allopathic treatments, but also proven amino acid, botanical, nutritional, antioxidant, and mucolytic complementary therapies, while keeping their eyes and minds open to new research and new therapies for this deadly disease.

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