Examples of GI Dysfunction and Malabsorption: Cystic Fibrosis

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Cystic Fibrosis

- Loss of function mutations in Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene lead to CF

- CFTR protein mediates secretion of chloride and bicarbonate across the epithelial layer

- Progressive obstructive lung disease is the most common cause of death

- In 2010, with best care, life into the 4th decade was possible

- Management involves maintaining pulmonary function and controlling infections

CF Foundation Care Centers

- 85% of US CF patients are managed in accredited CF Centers
- CFF mandates center personnel and pays each center by the number of patients it cares for each year
- CFF publishes evidence-based guidelines for CF care
- CFF scores every center every year based on many factors, including population pulmonary function, population BMI, and survival
- QI training and improvement projects are mandated for underperforming centers
Biological impact of CF on nutrition

More Calories expended:
- Increased pulmonary effort
- Chronic/recurrent inflammation
- CFTR mutations

Fewer Calories in:
- Poor appetite/intake
- Gastroparesis
- Prolonged small bowel transit
- Diminished sense of smell
- Abdominal pain
- Depression
- Poverty/Social chaos
- Behavioral problems
- Malabsorption
- Pancreatic insufficiency
- Poor adherence to enzyme therapy
- Impaired micelle formation
- Small bowel overgrowth
- Cystic fibrosis related diabetes
- Cystic fibrosis liver disease

Malnutrition

Other genetic factors

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Pancreatic insufficiency (PI)

• Pancreatic secretions digest the majority of protein, carbohydrate, and fat
• In CF, pancreas fibrosis begins in utero
• Most individuals with CF are PI at birth, and 85% will be PI by about one year of age
• Pancreatic enzyme replacement therapy (PERT) digests ~95% of fat with optimal use
Chronic intestinal inflammation

- Thick, dehydrated mucus layer in intestine
- Intestinal dysbiosis associated with both degree of CFTR impairment and antibiotic use
- Intestinal lesions include villous damage, ulceration, and edema
- Leads to diarrhea, bloating, nausea, abdominal pain, distention

Review: Dorsey and Gonska, J Cyst Fibros 2017
Decreased intestinal bicarbonate

- Pancreatic bicarbonate rapidly neutralizes gastric acid
- Enterocytes also produce bicarbonate
  \textbf{Both are impaired in CF}
- Bile salts, essential for mixed micelle formation, precipitate at low pH
- Optimum range for dissolving enteric coat of PERT is 5.5-6.0
- Intestine reaches neutral pH lower in the small bowel in people with CF than in normal

Borowitz, Ped Pulm 2015; Gelfond et al, Dig Dis Sci 2013
Intestinal pH in CF v. control

Gelfond et al, Dig Dis Sci 2013

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Liver disease

- Third leading cause of death in cystic fibrosis
- Most severe forms are focal biliary fibrosis and multilobular cirrhosis with or without portal hypertension
- Reduced bile salt formation leads to impaired mixed-micelle formation and reduced absorption

Review: Flass and Narkewicz, J Cyst Fibrosis 2013
Intestinal dysmotility

- CFTR may directly affect intestinal smooth muscle function
- Dysbiosis further impairs motility
- Results in overall slow intestinal motility
- Gastroparesis affects about a third
- Symptoms include nausea, early satiety, persistent dyspepsia, and abdominal pain

Review: Dorsey and Gonska, J Cyst Fibros 2017
Sinus disease

- Tenacious secretions obstruct sinus ostia leading to edema and bacterial infection
- Chronic sinusitis and recurrent nasal polyps are common
- Results in impaired sense of smell and thick retropharyngeal mucus
- Associated with reduced appetite

Cystic fibrosis related diabetes

• Affects up to 50% of people with CF over the lifespan
• Dominant cause is gradual loss of islet cell mass; but multifactorial
• Long, somewhat stuttering onset, impacted by inflammation
• Untreated CFRD is a catabolic state
• Decline in pulmonary function and body mass index seen several years before diagnosis

Moheet and Moran, Pediatric Pulmonology, 2017
Evidence for unique nutritional requirements in CF

• Most common cause of death is respiratory disease
• Maintenance of weight >50\textsuperscript{th} percentile for age and gender associated with longer survival
• Good nutritional management may result in an additional decade of life

Corey et al J Clin Epidemiol 1988
Nutrition and lung function in CF

- Prospective, observational study using data from the CFF Registry, 1989-1992
- 3142 patients with CF stratified by peak weight-for-age percentile (WAP) at age 4-5 years into 4 groups:
  - Less than 10th percentile
  - 10th to less than 25th percentile
  - 25th to less than 50th percentile
  - 50th percentile or greater

Results

• Patients with a WAP >50% at age 4 years reached a much higher height-for-age early in life and maintained this advantage into adulthood.

• Pulmonary function (FEV₁%predicted) was much lower in CF patients with WAP<10% at age 4 years. This finding tracked through age 18 years.
Survival highest in patients with better WAP at age 4 years

CF specific nutritional Interventions

• Newborn screening and early nutritional intervention
• High fat diet to increase calories (3 meals, 3 snacks, every day)
• Quarterly clinic visits with evaluation of growth and dietitian consult
• Water-miscible fat soluble vitamin supplementation

Growth failure

• Definition: low weight, losing weight, slow weight gain

• Early intervention
  – High-calorie oral supplementation
  – Behavioral/psychology counseling
  – Social services
  – Consultation with other services (GI and Endocrine)
  – Gastrostomy placement for supplemental feedings

Turck et al, Clin Nutr 2016; Schwarzenberg et al, J Cyst Fibros 2016
Fatty acids

• CF associated with
  – Linoleic acid
  – Docosahexaenoic acid
  – Variable changes in arachadonic, α-linolenic, and eicosapentaenoic acids

• Explanations include:
  – Fat malabsorption
  – Protein-energy malnutrition
  – Altered n-6 and n-3 fatty acid metabolism secondary to CFTR abnormality

Seegmiller, Int J Mol Sci 2014
Ivacaftor

- Improves the chances that the CFTR will be open
- Most effective in those with gating mutations (4-6%)
- Improves lung function and reduces sweat chloride
- Treatment leads to increased weight gain, possibly by improving release of bicarbonate into GI tract

Borowitz et al, Dig Dis Sci 2016
Research gaps

• What is the cause of dysbiosis and dysmotility in CF?
• What is the appropriate fat type for people with CF, to insure adequate EFA without increasing inflammatory products?
• How do we address nutrition as the patient ages and new complications occur?
• What is effect will modulators of CFTR have on nutrition?
Conclusions

• In CF, better early childhood nutrition is associated with better height growth, better lung function, and improved survival into adulthood.

• Optimal nutrition in CF is not a simple matter of increased calories, but attention to an disordered matrix of digestion, absorption, and intestinal function.
• END
Question

What is the impact of nutritional status in early life on the timing and velocity of height growth, lung function, complications of CF, and survival through age 18 years?
Potential complexities

• ~15% of people with CF are PS at birth; monitoring for gradual development of PI is crucial
• Pulmonary management involves many interventions and frequent antibiotics; appetite suppression and diarrhea may result
• Adolescence is a period of poor adherence to therapy