FAMILIAL CHYLOMICRONEMIA SYNDROME (FCS): MEDICAL NUTRITION THERAPY GUIDELINES FOR PATIENTS AND HEALTHCARE PROVIDERS

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BACKGROUND

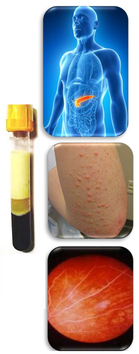
What is FCS?

Background:

- Rare autosomal recessive disorder (orphan disease) possibly 1:1,000,000, generally presenting early in life
- Severely elevated levels of plasma TGs, generally unresponsive to lipid-lowering therapies
- Caused by null *loss-of-function LPL, GPIHBP1, APOC2, APOA5, LMF1* gene mutations

Clinical Expression/Risk:

- Signs and symptoms:
- Plasma lactescence and viscosity
- Lipemia retinalis
- Abdominal pain
- Hepatosplenomegaly
- Eruptive xanthomas
- Recurrent acute pancreatitis (AP)
- Pancreatic insufficiency
- Decreased quality of life (QoL)



FCS: Treatment is Lifelong

- Current treatment is a lifelong extremely restrictive low fat diet, consisting of <20 grams fat or 15% total calories; exact fat intake goals should be provided on a individual basis upon estimated needs of the patient
- + MCT oil, no alcohol
- Short term treatment goal–immediate prevention/treatment of pancreatitis
  - Avoid: oral estrogens, diuretics, isotretinoin, glucocorticoids, Zoloft®, and beta-adrenergic blocking agents; fish oil supplements
  - Standard pancreatitis treatment, if necessary
- Long term treatment goals: Reduce risks of acute pancreatitis (AP) and increase quality of life (QoL)
  - Maintenance of triglycerides <2000 mg/dL through diet prevents pain, but <1000mg/dL is the goal
  - Ensure nutrient adequacy especially essential fatty acids, fat soluble vitamins and micronutrients
  - Avoid added sugars and limit simple carbohydrates
  - Address decreased quality of life (i.e underemployment, social isolation, depression)
- Currently no FDA approved treatment for FCS exists.
  - In some patients, elevated TGs and bouts of AP persist even with an extremely restricted low-fat diet
  - It is critical that patients and health care providers (HCPs) have clear dietary guidelines for the TX of FCS
  - Currently, limited dietary guidelines and resources for patients and HCPs are available on FCS

METHODS

Why and How a Working Group Came Together

- Patients with FCS struggle with many aspects of the need to follow a restrictive diet, not only in locating information on guidelines and adherence strategies, but also with its impact on social interactions and their well-being
- It became clear that there was limited information of these issues, both in terms of the scientific literature and patient guidance
- Registered Dietitian Nutritionists (RDNs) were interviewed to asses their expertise and interest in joining the expert group. Each RDN was assigned a topic in their area of expertise for development of the consensus report

The Registered Dietitian Nutritionist (RDN) Working Group

- RDNs met for a one day working group meeting to discuss and come to consensus on the dietary guidelines for patients with FCS
- Included in the group was a patient with FCS
- Individual presentations by all faculty members were compiled to produce dietary guidelines for patients with FCS across the lifespan

Goals and Objectives:

- Establish dietary guidelines for patients with FCS across the lifespan
- Publication of guidelines
- Create educational dietary resources for HCPs

RECOMMENDATIONS & DISCUSSION

Dietary Management of FCS

- Very low-fat diet (10-15% of calories from fat)
- Meet requirements for essential fatty acids (EFAs)- omega 6 and omega 3
- Low in simple carbohydrates; limit total carbs
- Choose carbs with fiber
- Eliminate alcohol
- Meet nutrient recommendations
- Meet needs for co-morbidities
- Recipes for personal, ethnic and cultural preferences
- Weight management and physical activity
- Balance calories
- Enjoy your food prepared with no fats or with prescribed MCT oil

- ***Foods to Increase***
  - *Vegetables (half your plate)*
  - *Whole grains and legumes*
  - *Switch to fat-free milk and fat-free dairy products*
- ***Foods to Avoid***
  - *Fat-containing foods, refined starches, sugars*
  - *Sugary drinks; drink water instead*
  - *Alcohol*

Dietary Management of FCS in Pediatrics

- Meet estimated nutrient needs for appropriate growth.
- Very low fat diet (10-15% as tolerated)
- Low in simple carbohydrates; limit total carbohydrates
- May limit dietary fat to EFA needs per patient tolerance
  - EFA: 2-4% daily kcal from ALA and LA– an RDN can estimate specific needs
- MCT supplementation as needed to increase dietary fat intake and macronutrient composition of diet
- Supplemental LCT and fat soluble vitamins may be provided as needed to prevent deficiencies.
  - Triene:Tetraene ratio may be utilized to monitor for EFA deficiency
- Analysis of food records may be helpful to determine macro- and micronutrient intakes
- Families may utilize smart phone applications to monitor diet as needed
- Monitor growth trends on appropriate growth chart
  - WHO growth charts recommended 0-24 months of age
  - CDC growth charts recommended 2-20 years of age

- Age-appropriate nutrition
  - 0-12 months: Low LCT, high MCT formula or skimmed and fortified expressed breast milk. (See table to the right with sample comparison of formulas and human milk.) Introduce low fat table foods when age-appropriate.
  - 12-24 months: skim milk and low fat table foods as appropriate. Avoid concentrated sweet, including 100% fruit juice.
  - Children and adolescents: continue to provide individualized counseling and modify diet as needed. Special considerations include picky eating in children and compliance in adolescents.

Sample Comparison of Two Low Fat Formulas, Term Human Milk, and a Standard Infant Formula

Formula Manufacturer (kcal/ml)	Grams/100mL (% kcals)			% Fat as MCT	Comments
	CHO	Fat	Protein		
Monogen® Nutricia (22 kcal/30 mL) Recommended	12 (64%) corn syrup solids	2.1 (25%) fractionated coconut oil, walnut oil	2.2 (11%) whey protein concentrate (milk, soy lecithin), free amino acids	90%	• Approved for children over 1 year of age. • Ratio of essential fatty acids: N6:n3 ratio of 4.6:1. • Provides recommended intake of vitamins and minerals, including trace elements. • Available in powder only. • Contains 203mg per 100 kcals as linoleic acid and 38.3mg per 100 kcals as alpha-linolenic acid.
Enfaport® Mead Johnson (30 kcal/30 mL) Recommended	10.2 (40) corn syrup solids	5.6 (46) MCT and soy oils, DHA, ARA	3.6 (14) calcium and sodium caseinates (from milk)	84%	• Approved for infants. • Ratio of essential fatty acids: N6:n3 ratio of 2:1. • Nutritionally complete at 30kcal/30mL. Can be diluted to lower concentration. • Available in ready-to-feed only. • Contains 350mg per 100 kcals as linoleic acid.
Human milk, term (20 kcal/30 mL) Recommended w/ modification	8 (47) lactose	3.5 (47) human milk	0.9 (5) human milk (mostly whey)	Variable	• Nutrient content varies among women. • Not recommended for FCS unless skimmed and fortified to meet essential fat and MCT needs.
Similac ® Advance Abbott Nutrition (19 kcal/30 mL) Not Recommended	6.9 (42) lactose, galacto-oligosaccharides (GOS)	3.6 (50) high oleic safflower, soy and coconut oils, DHA, ARA	1.3 (8) nonfat milk and whey protein concentrate	Unknown	• Portion of fat from coconut oil, providing unknown %MCT. • Standard infant formula. • Available in powder and ready-to-feed. • Not recommended for FCS due to high fat and low MCT content.

*Note: **Not an all-inclusive list.** Please consult a Registered Dietitian Nutritionist to recommend the most appropriate formula for each patient on an individualized basis.

Chronic Pancreatitis

- Chronic inflammation of the pancreas, which causes permanent damage
- Symptoms: abdominal pain, oily stools, weight loss, indigestion
- Functional changes
  - Exocrine: nutrient digestion and absorption
  - Endocrine: glucose intolerance and diabetes
- Increases risk for malnutrition
  - Malabsorption of nutrients
  - Increased metabolic activity
  - Steatorrhea
- Fatigue may impact eating habits and ability to cook or shop for food

Additional Recommendations

- **For patients & caregivers**
  - Patients may benefit from ongoing nutrition counseling throughout the life cycle
  - Therapy to address psychosocial concerns (i.e., depression/anxiety)
  - Creation of educational tools/resources to provide information on the importance of diet for the lifelong management of FCS
  - Connect with other patients (FCS foundation-provide link)
- **For healthcare professionals**
  - Published guidelines
  - CME/CEU programs
  - Multidisciplinary work with RDN, lipidologist, and pancreatologists/GI

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DISCLOSURES

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Lori Alexander is a consultant for Akcea Therapeutics and received an honorarium for her participation in the RD Working Group from Akcea Therapeutics

Lauren Williams is a consultant for Akcea Therapeutics and received an honorarium for her participation in the RD Working Group from Akcea Therapeutics

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Kathy Rhodes received an honorarium for her participation in the RD Working Group from Akcea Therapeutics

Wahida Karmally is a consultant for Akcea Therapeutics and received an honorarium for her participation in the RD Working Group from Akcea Therapeutics

Lindsey Sutton received an honorarium for her participation in the RD Working Group from Akcea Therapeutics

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Characterizing Familial Chylomicronemia Syndrome: Baseline data of the APPROACH Study

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Background/Synopsis: Familial Chylomicronemia Syndrome (FCS) is a rare, recessive genetic disorder caused by mutations in Lipoprotein Lipase (LPL) or genes required for LPL functionality. FCS is characterized by hyperchylomicronemia, recurrent abdominal pain, hepatosplenomegaly and recurrent episodes of acute pancreatitis that may result in pancreatic insufficiency. There are no FDA approved treatments for FCS and patients are managed with a low-fat diet. Due to the rarity of FCS there are few case series describing phenotypic variability in this disorder.

Objective/Purpose: To describe demographic and clinical characteristics of adult FCS patients enrolled in a clinical trial.

Methods: We analyzed baseline data from 67 patients with FCS, participating in a Phase III study of volanesorsen (apoC-III antisense oligonucleotide).

Results: Sixty-seven patients with a mean age of 46±13 years were enrolled. In 54 patients (80%) the diagnosis was confirmed genetically with LPL mutations accounting for 41 (81%) cases. The median age (P25, P75) at diagnosis was 27 (15, 36) years. Fifty four percent were female and 81% were Caucasian with a mean body mass index of 24.9±5.7 kg/m^2. Median fasting TG (P25, P75) were 2012 (1247, 3117) mg/dL despite 43% of patients receiving fibrates, 27% fish oils and 21% statins. Eruptive xanthomas and lipemia retinalis were identified in 15 (22%) and 14 (21%) of patients, respectively. Forty-nine patients (73%) had a documented history of acute pancreatitis and among those, 27 patients experienced 83 pancreatitis events within the past 5 years. Twenty five percent of patients (17 out of 67) reported abdominal pain events during the 6-8 week screening period. Magnetic resonance imaging demonstrated that liver and splenic volumes were increased and that splenic volume had a mild inverse correlation with platelet counts (r=-0.1200, p=0.0052). Postprandial TG clearance was severely impaired (Figure).

Conclusions: Our data confirm that TGs remain significantly elevated in most FCS patients despite dietary restrictions and TG-lowering therapies and that FCS is frequently complicated by acute pancreatitis. A relatively late age of diagnosis suggests a likely under diagnosis and appreciation of this rare genetic disorder.

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Familial Chylomicronemia Syndrome (FCS): Medical Nutrition Therapy for Patients and Providers

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Lead Author's Financial Disclosures: None

Study Funding: Akcea Therapeutics supported the expert group with conference calls and a live meeting, and all content was developed independently by the expert committee.

Background/Synopsis: FCS is a rare autosomal recessive disorder due mainly to loss of function mutations of lipoprotein lipase. This results in severe elevation of triglycerides (TG) and massive accumulation of chylomicrons in plasma, often leading to pancreatitis. This underdiagnosed disorder causes decreased quality of life (QoL) and increased ER visits and hospitalizations. Many FCS patients live in isolation, experience employment difficulties and have trouble socializing due to its consequences.

Objective/Purpose: An unmet need came out of an FCS expert committee of Registered Dietitians/Nutritionists (RDNs) and patients, sharing challenges and adherence to dietary restrictions, meeting nutrient requirements and improving QoL. The aim was to share best practices, and ultimately provide tools and relevant resources to support patients, caregivers and healthcare professionals, and raise awareness of the dietary impact of managing the disease.

Methods: RDNs were interviewed to assess their expertise and interest in joining the expert group. Each RDN was assigned a topic in their area of expertise for the development of the consensus report. A patient with FCS was also included in the group to provide a personal perspective of the challenges of living with FCS. The report included patient-centered nutrition recommendations to optimize nutritional needs to manage and prevent complications of FCS. The report also provided resources for healthcare professionals. Topic-specific presentations were developed for future education.

Results: The RDN expert committee incorporated topic-specific presentations into a consensus report on diet and FCS. Topics provided current information on FCS, pancreatitis, implementing current nutrition recommendations,

supporting patients with adherence to a very low fat diet, pediatric management of FCS, pharmacologic therapies available and in development, and personal experiences of a patient diagnosed with FCS in infancy.

Conclusions: This report adds valuable resources to the limited information currently available to assist patients with FCS and healthcare providers. The dissemination plans for this report include submitting a manuscript for publication, developing web-based CEU programs to "Train the Trainer", employing patient education resources such as recipes and FCS Foundation blog participation, and providing resources for support groups.

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PCSK-9i Gender Study

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Lead Author's Financial Disclosures: None

Study Funding: None

Background/Synopsis: Due to residual risk in patients unable to achieve LDL goals with maximum tolerated statin doses, coronary heart disease still remains the leading cause of death in both men and women. In 2015, monoclonal antibody therapy to reduce PCSK9 activity at the surface of the hepatocyte was approved. PCSK9 blocking antibodies can reduce LDL-C up to 70% beyond levels achieved with statin therapies alone.

Objective/Purpose: To examine the significance of an observational trend observed in multiple lipid clinic sites that indicate a more robust drop in LDL-C in men verses women with both alirocumab and evolocumab.

Methods: A retrospective chart review was conducted with data collected from several lipid clinics in Florida. A one page data collection form was developed during the initial pilot study. The primary endpoint was to quantify gender differences in LDL-C lowering in PCSK-9 inhibition (aggregate, alirocumab and evolocumab). Secondary endpoints included (1) gender differences in LDL-C response to PCSK-9 inhibition (aggregate, alirocumab and evolocumab) in patients on non-zero vs. zero tolerated statin dose (2) gender differences in LDL-C response to PCSK-9 inhibition (aggregate, alirocumab and evolocumab) in patients based on age and (3) gender differences in LDL-C response to PCSK-9 inhibition (aggregate, alirocumab and evolocumab) in patients based on baseline LDL-C levels.

	Men	n	Women	n	Delta	p-value
AGG	61.4	46	49.2	51	12.2	.002
P	54.8	19	43.4	28	11.4	.042
R	66.2	25	55.6	23	10.6	.063

Results: Results and Conclusions: Data was collected from 5 lipid clinics with a sample size of 97 patients. Conclusions from the 4 data analysis revealed the following: (1) Men have a statistically significantly greater LDL-C reduction than women. LDL-C Reduction (% from baseline):
(2) Except for the eldest cohort, the trend for men getting a greater reduction across age quintiles is consistent. {note that the n's in each group are low making it difficult to reach statistical significance} (3) Regardless of baseline LDL the men / women differential persists, although the n's in each group are too small to reach statistical significance. (4) The differences in LDL-C lowering between men and women are due to those patients on concommitent statin therapy.

Conclusions: Implications: Should a more aggressive approach to lipid management with PCSK9-I be considered in women who show a less robust response to therapy. Will these gender results be relevant in outcome studies available later this year?

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Familial Chylomicronemia Syndrome (FCS) Patients Recruited to the APPROACH Trial of Volanesorsen Therapy are Representative of Subjects with FCS

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Study Funding: APPROACH study was funded by Akcea Therapeutics a subsidiary of IONIS pharmaceuticals

Background/Synopsis: FCS is a rare autosomal recessive disease due to markedly reduced lipoprotein lipase activity. Because of lack of effective therapy, FCS is associated with a greater burden of disease and mortality compared with other hypertriglyceridemic disorders. A seminal pilot study demonstrated that inhibiting apoC-III using the antisense oligonucleotide volanesorsen was a potentially highly effective therapy. The APPROACH Trial