Familial Chylomicronemia Syndrome (FCS)

Presentation Overview

- What is familial chylomicronemia syndrome (FCS) and how does it differ from other types of severe HTG?
- What is the pathophysiology of severe HTG and FCS?
- What are the adverse consequences of severe HTG (with or without FCS) and what is their pathophysiology?
- How should FCS be diagnosed?
- How should FCS be management?

What's in a Name? Common Synonyms for Familial Chylomicronemia Syndrome

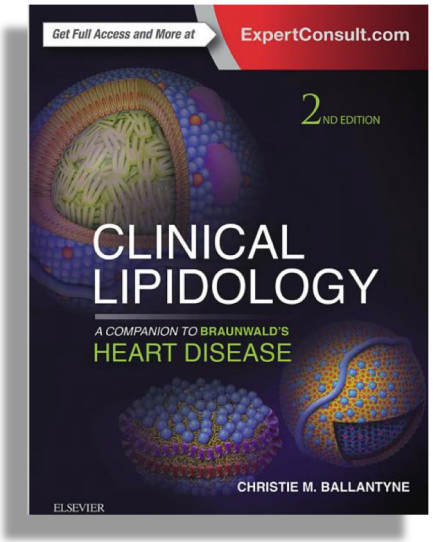
- Chylomicronemia syndrome
- Chylomicronemia, familial
- Familial chylomicronemia
- Hyperchylomicronemia, familial
- Familial hyperchylomicronemia
- Hyperlipoproteinemia type I
- Fredrickson Type I Hyperlipidemia
- Hyperlipoproteinemia type IA
- Exogenous hypertriglyceridemia
- Familial fat-induced hypertriglyceridemia
- Familial LPL deficiency
- Lipoprotein lipase deficiency (LPLD)
- Lipase D deficiency
- Hyperlipemia idiopathic Burger-Grutz type
- Burger-Grutz syndrome

Abbreviation: LPL=familial lipoprotein lipase.

The National Pancreas Foundation website https://pancreasfoundation.org/patient-information/ailments-pancreas/familial-chylomicronemia-syndrome/ . 2018.

Prevalence of FCS

Prevalence estimates cited in literature and by organizations...



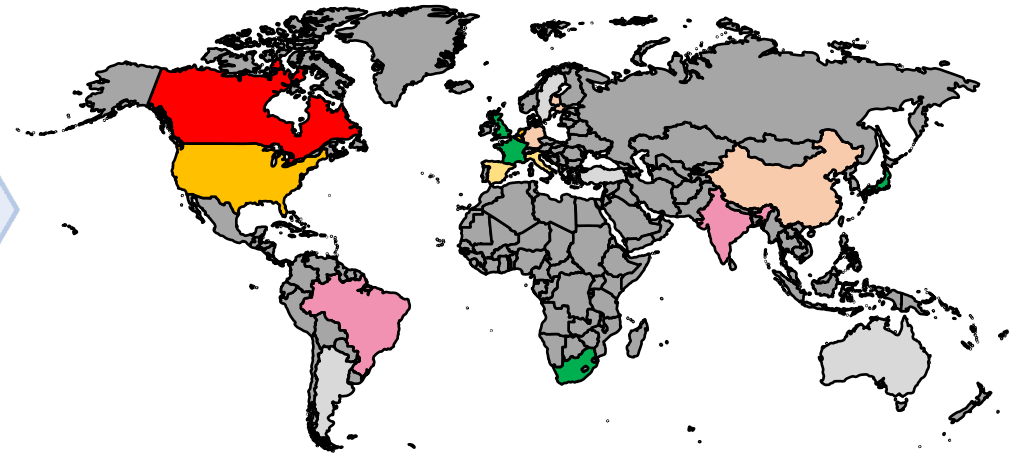
1:1,000,000[1]

NORD®
National Organization for Rare Disorders

1:250,000[3]

Founder Population and Its Relation to Prevalence of FCS[1,2]

- Prevalence in populations with founder effect is higher than overall (generalized) prevalence



Abbreviation: FCS=familial chylomicronemia syndrome

1. Kastelein JP. *NORD.* (2015) https://rarediseases.org/physician-guide/lipoprotein-lipase-deficiency-lpld/.
2. Ballantyne, C. et al. *Clinical Lipidology:A Companion to Braunwald's Heart Disease.* **2nd ed.** Elsevier;Saunders; 2014.
3. Kastelein JP. *NORD.* (2016) https://rarediseases.org/physician-guide/familial-lipoprotein-lipase-deficiency/.

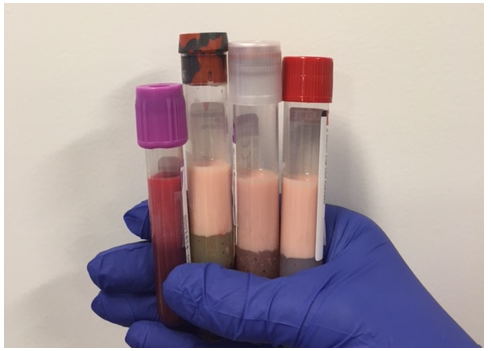
What Is FCS?

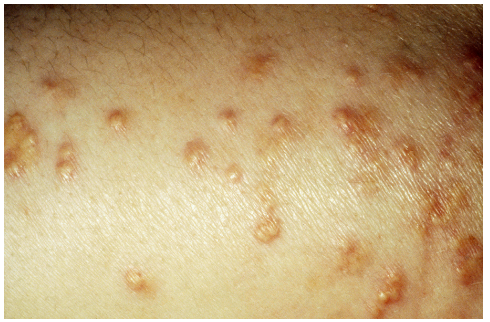
Background:

- Rare autosomal recessive disorder[1]
- Severely elevated levels of plasma TG, generally unresponsive to TG-lowering medications[1-3]

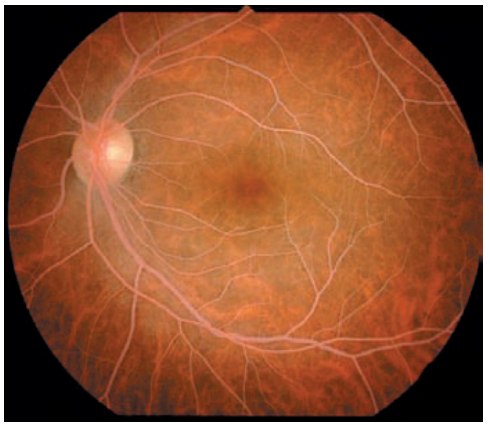
Clinical Expression/Risk[3]

- Signs and symptoms:
  - Eruptive xanthomas
  - Plasma lactescence and increased viscosity
  - Lipemia retinalis
  - Hepatosplenomegaly
  - Abdominal pain (w/ or w/o acute pancreatitis)
- Hospitalization for acute pancreatitis (often recurrent) w/ or w/o evidence of chronic pancreatitis
- Pancreatic exocrine and/or endocrine insufficiency





Biophoto Associates / Science Source



Abbreviations: FCS=familial chylomicronemia syndrome; TG=triglycerides.

1. Brahm AJ, et al. *Nat Rev Endocrinol.* (2015) 11:352-362. doi:10.1038/nrendo.2015.26.
2. Toth PP, et al. *Atherosclerosis.* (2014) 237(2):790-797. doi:10.1016.
3. Burnett JR, et al. *Gene Reviews.* Seattle, WA: University of Washington; (1999) http://www.ncbi.nlm.nih.gov/books/NBK1308/?report=printable.

Familial Chylomicronemia Syndrome – Clinical/ Differential Diagnosis

- Severe fasting HTG (>10 mmol/L or 880 mg/dL)[4,5]
- Refractory to standard TG therapies)[5]

Exclude/Control

Other Causes of HTG:[4]
- Alcohol excess
- Uncontrolled T2DM
- Medications and medical conditions known to raise TG*

Potential FCS if any of the following:

History of acute pancreatitis[1-3,7]

or

History of **recurrent abdominal pain**[1-3,7] w/o other known cause

or

Confirmation by **genetic analysis**[1-6] (mutations in LPL, apoCII, GPIHBP1, ApoA5 or LMF1)

FCS

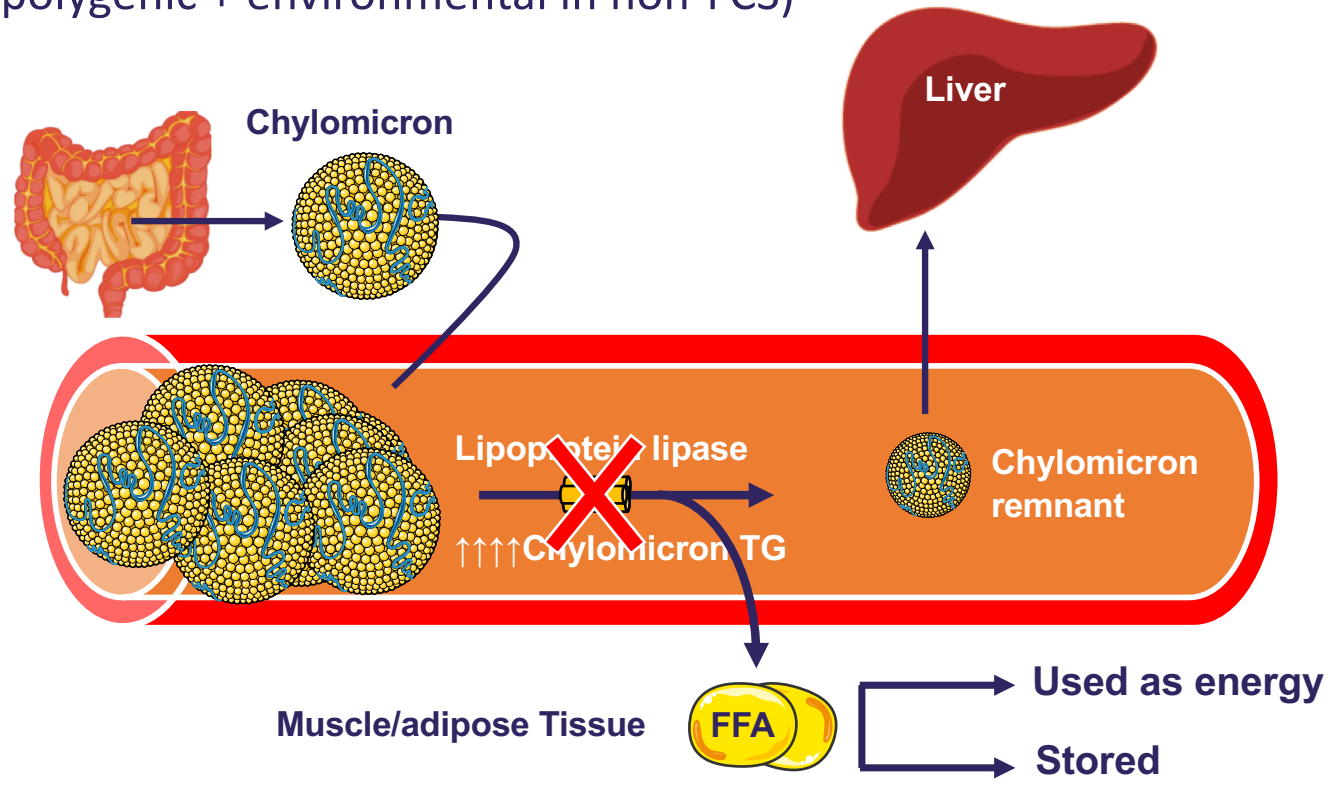
* oral estrogen, exogenous glucocorticoids, 2nd generation antipsychotics, Isotretinoin, antiretrovirals/protease inhibitors, HIV, Cushing syndrome, nephrotic syndrome, renal insufficiency

Abbreviations: FCS=familial chylomicronemia syndrome; TG=triglycerides; HTG=hypertriglyceridemia; T2DM=Type 2 diabetes; apoCII=apolipoprotein C2; GPIHBP1=glycosylphosphatidylinositol; ApoA5=apolipoprotein A-V; LMF1=lipase maturation factor 1.

1. Carpentier AC, et al. *J Clin Endocrinol Metab.* (2012) 97(5):1635-1644.
2. Burnett JR, et al. *GeneReviews.* Seattle, WA: University of Washington; (1999) http://www.ncbi.nlm.nih.gov/books/NBK1308/?report=printable.
3. Gotoda T, et al. *J Atheroscler Thromb*. (2012) 19(1):1-12.
4. Brahm A, et al. *Nat Rev Endocrinol. (*2015) 11(6):352-362.
5. Surendran RP, et al. *J Intern Med.* (2012) 272(2):185-196.
6. Berge KE, et al. *Atherosclerosis.* (2014) 234(1):30-33.
7. Overgaard M. *Ann Clin Biochem*. (2013) 50(Pt 4):374-379.

FCS Pathophysiology

- Chylomicronemia: pathological persistence of chylomicrons in plasma following a fasting period of 10 to 14 hours[1,2]
- Fasting chylomicronemia is always caused by defective chylomicron processing (monogenic in FCS, polygenic + environmental in non-FCS)[2]



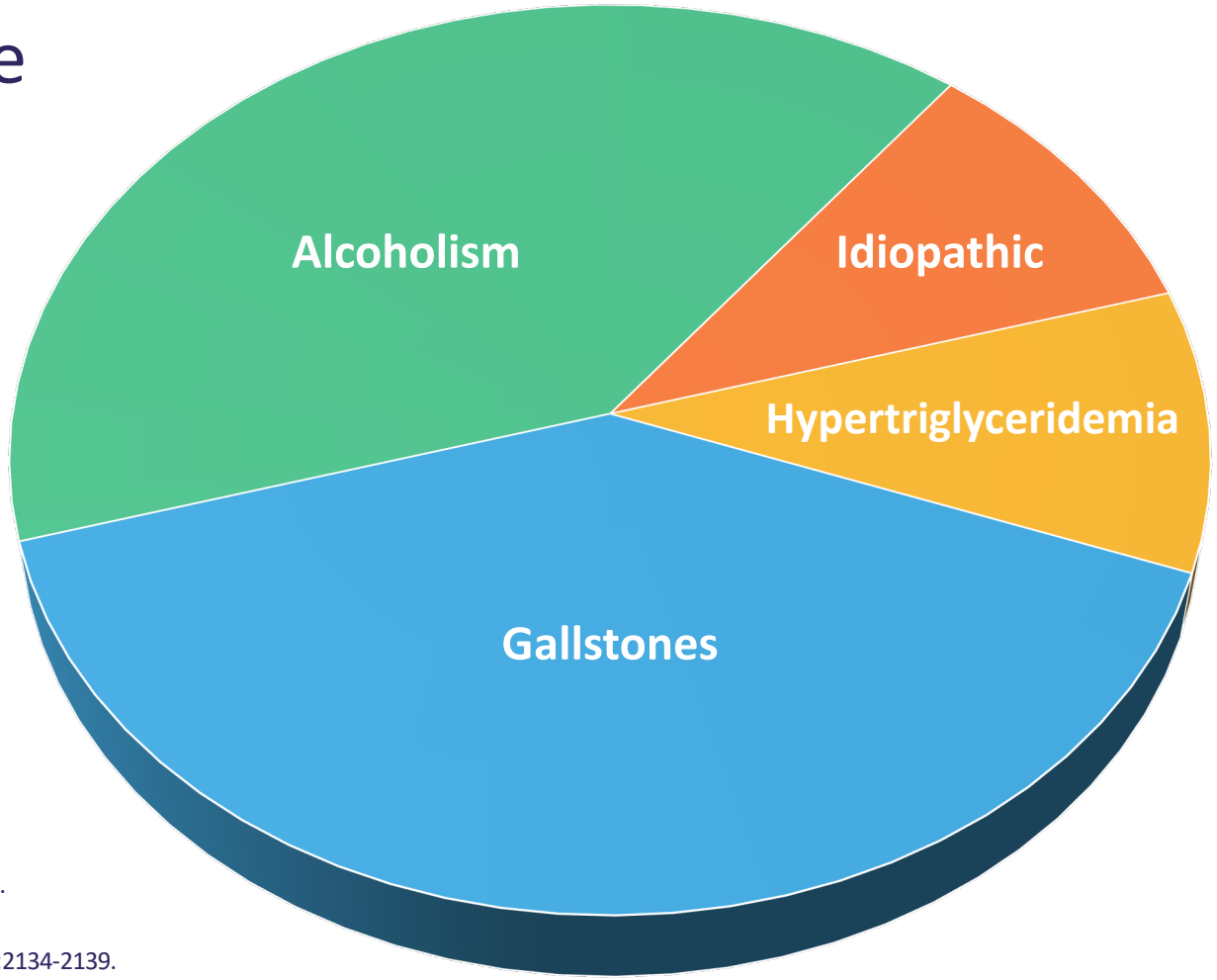
Adapted from Braham, *Nat Rev Endocrinol,* 2015.

Abbreviations: FFA, free fatty acid; TG, triglyceride; VLDL, very low-density lipoprotein; FCS=familial chylomicronemia syndrome.

1. Brunzell JD, et al. *Med Clin North Am. (*1982) 66(2):455-468.
2. Brahm A, et al. *Nat Rev Endocrinol. (*2015) 11(6):352-362.

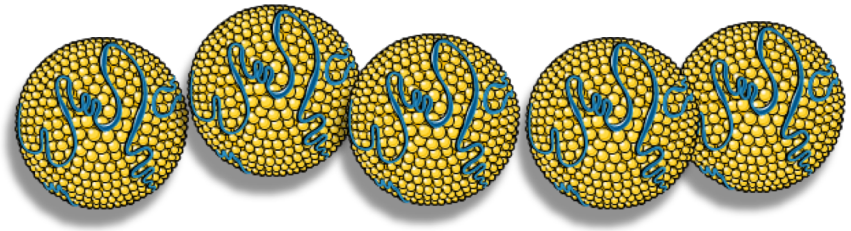
Hypertriglyceridemia Is the Third Leading Cause of Acute Pancreatitis

- Causes of acute pancreatitis:[1-4]



1. Whitcomb DC. *NEJM*. (2006) 354:2142-2150.
2. Valdivielso P, et al. *Eur J Med. (*2014) 25:689-694.
3. Ewald, N. *ClinicalLipidology.* (2013) 8:5, 587-594
4. Fortson MR, et al. *Am J Gastroenterol. (*1995) 90:2134-2139.

Likely Mechanisms of Acute Pancreatitis in Severe HTG



Large Triglyceride-Rich Chylomicrons

Pancreatic-lipase leak (Acinar cells)
→↑↑↑local FFA prod.

Impaired pancreatic blood flow[2]

→↑↑lipase leak[1]
(& ↑Trypsinogen?)
↑↑↑local FFA prod…

Ischemia/acidosis[2]

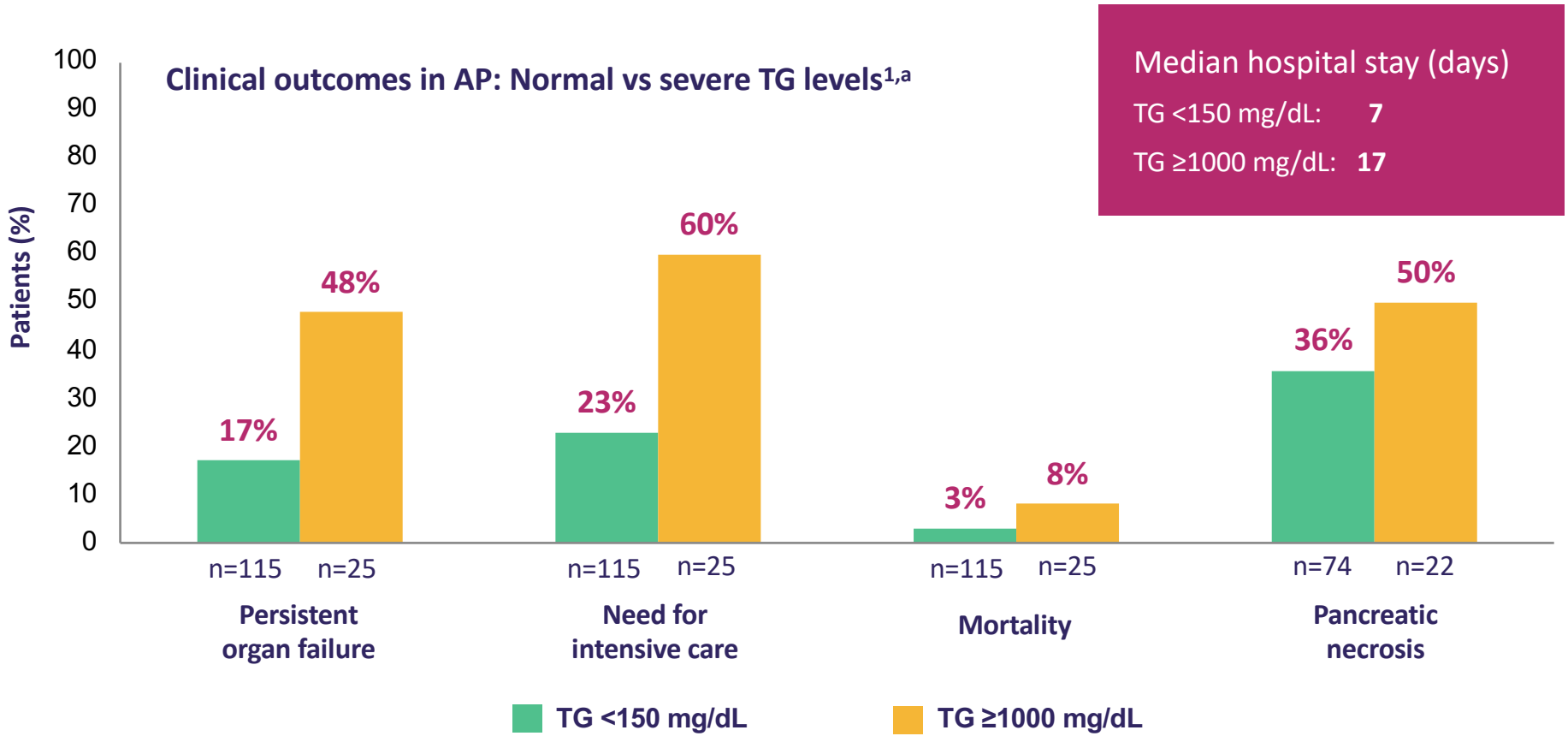
Pancreatic acinar cell injury[2]

Acute Pancreatitis[2,3]

Abbreviation: FCS=familial chylomicronemia syndrome.

1. Gan SI, et al. *World J Gastroenterol.* (2006) 12:7197-7202.
2. Valdivielso P, et al. *Eur J Med.* (2014) 25:689-694.
3. Khokar AS, et al. *Nutr Clin Pract.* (2004) 19:5-15.

Acute Pancreatitis (AP) has Far *Worse* Outcomes in Patients with Severe HTG



Median hospital stay (days)

TG <150 mg/dL: **7**

TG ≥1000 mg/dL: **17**

Adapted from Nawaz, *Am J Gastroenterol*, 2015.

Abbreviations: HTG=hypertriglyceridemia; TG=triglyceride.

1. Nawaz H, Koutroumpakis E, Easler J, et al. Elevated serum triglycerides are independently associated with persistent organ failure in acute pancreatitis. *Am J Gastroenterol.* (2015) 110(10):1497-1503. doi:10.1038/ajg.2015.261.

a. Patients were neither evaluated or diagnosed with FCS.[1]

Patient Profile/Natural History of FCS

Presentation during infancy, childhood, during pregnancy, and as adults is described.

- **~25% develop symptoms in infancy,[1] including failure to thrive**[2]
- **Some individuals show *no* symptoms until *adulthood***, often presenting with abdominal pain, at which time possibility of a genetic cause may be overlooked[3]
- Even though the genetic defect is present from birth, **FCS may first present during pregnancy**, when severe HTG (fasting chylomicronemia) and acute pancreatitis first emerge[5]
- **Large individual variation in presentation and course.** Genetic causes vary in severity as do presence and impact of secondary factors (e.g. diet, obesity, diabetes, alcohol intake). FCS (monogenic) tends to have more striking HTG and more severe clinical presentation than polygenic but there is considerable overlap in TG levels[2,4]

Abbreviations: BMI=body mass index; FCS=familial chylomicronemia syndrome; LPL=lipoprotein lipase.

1. Burnett JR, et al. *GeneReviews.* Seattle, WA: University of Washington; (1999) http://www.ncbi.nlm.nih.gov/books/NBK1308/?report=printable .
2. Brahm A, et al. *Nat Rev Endocrinol. (*2015) 11(6):352-362.
3. Gotoda T, et al. *J Atheroscler Thromb*. (2012) 19:1-12.
4. Chokshi SP, et al. *J Clin Lipidol.* (2014) 8(3):287-295.
5. Basar R, et al. *Arch Gynecol Obstet.* (2013) 287(5):839-843.

FCS Management Goals

Reduce plasma TG levels as much as possible

Prevent recurrent abdominal pain/acute pancreatitis and other sequelae

Alleviate signs and symptoms/physical manifestations of FCS[1,2,3]

Reduce risk of long-term consequences (chronic pancreatitis, etc.) and death[1,4,5]

Abbreviation: FCS=familial chylomicronemia syndrome.

1. Kastelein JP. *NORD.* (2015) https://rarediseases.org/physician-guide/lipoprotein-lipase-deficiency-lpld/.
2. Burnett JR, et al. *GeneReviews.* Seattle, WA: University of Washington; (1999) http://www.ncbi.nlm.nih.gov/books/NBK1308/?report=printable.
3. Afari ME, et al. *R I Med J* (2013). (2015) 98(12):40-43.
4. Brahm AJ, et al. *Nat Rev Endocrinol. (*2015) 11:352-362. doi:10.1038/nrendo.2015.26.
5. Jacobson TA, et al. *J Clin Lipidol. (*2015) 9(2):129-169. doi:10.1016/j.jacl.2015.02.003.

Management of FCS: Dietary Guidance

- Strict lifelong dietary restrictions:[1,2,4]
- Extreme low-fat diet (≤15% of energy)[3]
- Complete avoidance of alcohol[3,4]
- Some restriction of sugar intake also adviseable[5]

Although extremely difficult to follow, these dietary therapies can improve clinical manifestations[1-5]

Reduced abdominal pain[4]
Reduced risk of xanthomas[3]
Reduced risk of acute pancreatitis[1-4]

Abbreviation: FCS=familial chylomicronemia syndrome.

1. Brahm AJ, et al. *Nat Rev Endocrinol. (*2015) 11:352-362. doi:10.1038/nrendo.2015.26.
2. Jacobson TA, et al. *J Clin Lipidol. (*2015) 9(2):129-169. doi:10.1016/j.jacl.2015.02.003.
3. Kastelein JP. *NORD.* (2015) https://rarediseases.org/physician-guide/lipoprotein-lipase-deficiency-lpld/ .
4. Pouwels ED, et al. *S Afr Med J. (*2008) 98(2):105-108. doi:10.7196/SAMJ.424.
5. Berglund L, et al. *J Clin Endocrinol Metab. (*2012) 97(9):2969-2989. doi:10.1210/jc.2011-3213.

FDA-Approved Drugs Indicated To Lower Triglycerides

Fibrates[1,2*]	Rx Omega-3[3,4*]	Niacin[5*]	Statins[6,7]
• ↑LPL activity →↑lipolysis and clearance of TG-rich lipoproteins • ↓hepatic VLDL production (indirectly →↓LDL production) • ↓DGAT activity →↓hepatic TG synthesis • ↑HDL production • ↓HDL catabolism	• ↑LPL activity →↑lipolysis and clearance of TG-rich lipoproteins • ↓DGAT activity →↓hepatic TG synthesis • ↑hepatic TG β-oxidation →↓hepatic TG content	• ↑LPL activity →↑lipolysis and clearance of TG-rich lipoproteins • ↓hepatic VLDL production (indirectly →↓LDL production) • ↑HDL production • ↓HDL catabolism • ↓FFA release from adipose tissue	• ↓hepatic cholesterol synthesis →↑hepatic LDL receptors to ↑LDL uptake/catabolism • ↓hepatic VLDL production (indirectly →↓LDL production) • Possible ↑lipoprotein lipase activity

FCS patients are generally unresponsive to all available TG-lowering therapies[8]

*Proposed; exact mechanisms may not be fully delineated.

Abbreviations: FDA=food and drug administration; FCS=familial chylomicronemia syndrome; DGAT=diacylglycerol acyltransferase; HDL-C=high-density lipoprotein cholesterol; LDL=low-density lipoprotein; TG=triglyceride; VLDL=very low-density lipoprotein; VLDL-C=very low-density lipoprotein cholesterol.

1. TRICOR [package insert]. North Chicago, IL: AbbVie Inc; 2016;
2. LOPID [package insert]. New York, NY: Parke-Davis; 2010.
3. VASCEPA [package insert]. Bedminster, NJ: Amarin Pharma Inc; 2015.
4. LOVAZA [package insert]. Research Triangle Park, NC: GlaxoSmithKline, 2014.
5. NIASPAN [package insert]. North Chicago, IL: AbbVie Inc; 2015.
6. CRESTOR [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2015.
7. LIPITOR [package insert]. New York, NY: Parke-Davis; 2012.
8. Burnett JR, et al. *GeneReviews.* Seattle, WA: University of Washington; (1999) http://www.ncbi.nlm.nih.gov/books/NBK1308/?report=printable.

Emerging Therapy for FCS

- Apo C-III inhibits LPL activity and is strongly associated with HTG. (also may inhibit hepatic uptake of TG-rich lipoproteins and may have direct pro-atherogenic effects)
- An anti-sense oligonucleotide for apo C-III (volanesorsen, Akcea) blocks hepatic apo C-III synthesis
- When tested in 3 FCS patients, volanesorsen decreased apo C-III by 80%, and unexpectedly lowered fasting plasma TG by a mean of 73% (1,511 mg/dL)
- Volanesorsen then began clinical development for FCS. Results so far:
  - Efficacy
  - ↓TG by 50-73%
  - ↓Apo C-III by ~70-90%
  - ↓Acute pancreatitis (1 event w/ volanesorsen vs 4 events w/ placebo) and
  - ↓Severe abdominal pain (15% of patients w/ volanesorsen vs 24% w/ placebo)
  - Safety
  - ↓ platelet counts in 16 of 33 patients on volanesorsen vs 1 of 33 on placebo
  - Thrombocytopenia (< 25,000 plts/mm^3) in 4 of 33 vs 0 of 33 patients (volanesorsen vs placebo, respectively)
  - No bleeding episodes noted
- FDA *rejected* volanesorsen approval (Aug '18) due to safety concerns
- Akcea is conducting additional trials of volanesorsen for re-submission to FDA

Abbreviations: FCS=familial chylomicronemia syndrome; FDA=food and drug administration; RNA=ribonuclease.

Al Idrus, A. (2018)
https://www.fiercebiotech.com/biotech/split-vote-fda-adcomm-backs-akcea-ionis-volanesorsen .

Conclusions

- FCS is a rare autosomal recessive disorder, which causes severe HTG which is generally unresponsive to available lipid-lowering medications
- Severe HTG in FCS (and from polygenic + secondary causes) can cause acute pancreatitis
- Acute pancreatitis associated with severe HTG has a worse prognosis than pancreatitis w/o severe HTG
- Strict dietary restriction (fat and alcohol) is the only available management option for FCS (minor benefit possible from orlistat) at present
- A new drug, volanesorsen, an apolipoprotein C-III (ApoC-III) inhibitor, is in late-stage clinical development for treatment of FCS

Abbreviations: FCS=familial chylomicronemia syndrome; TG=triglyceride.