# Management of Hospitalized Children with Severe Hypertriglyceridemia

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**ABSTRACT**

Severe hypertriglyceridemia (SHTG) is uncommon in children. Those with triglyceride (TG) levels greater than 1,000 mg/dL are likely to have a monogenic disorder affecting TG metabolism or a combination of polygenic and small-effect genetic variants that increase the risk of hypertriglyceridemia (HTG), in addition to other factors such as obesity and insulin resistance, poorly controlled diabetes, or medications that interfere with TG metabolism. When present, SHTG is associated with an increased risk of acute pancreatitis and, long-term, may contribute to ASCVD-related morbid and premature mortality. In 2011 the NHLBI Expert Panel published recommendations for clinical management of children with HTG in the ambulatory setting (1). Presently, however, there are no pediatric guidelines to assist clinical decision-making when aggressive therapy of SHTG in critically ill children who require hospitalization, with or without pancreatitis, might be indicated. In this article we focus on the inpatient management of SHTG. Other Endotext chapters address genetic and secondary causes of HTG and the outpatient management of these disorders (2-5).

## INTRODUCTION

Severe HTG is uncommon in children but is most commonly encountered in youth who are obese and insulin resistant, those who have poorly controlled diabetes, or who require medications that interfere with TG metabolism (Table 1). Although rare, those with monogenic disorders have severe elevations of TG, typically >1000 mg/dL, while those with polygenic and small-effect genetic variants that contribute to alternations in lipid and lipoprotein metabolism are more common and in combination with secondary causes of HTG can lead to TG levels >1000 mg/dL (Table 2 and 3). Such severe elevations may cause significant morbidity, including pancreatitis, and occasionally may be life-threatening, necessitating aggressive TG lowering.

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| **Table 1. Common Secondary Causes of Dyslipidemia** | |
| **Condition** | **Screening Tests** |
| Hypothyroidism  Liver Diseases  Kidney diseases  Diabetes Mellitus  Obesity / Insulin Resistance | Free T4, TSH  CMP  CMP/ UA  CMP/ UA/Fasting or Random Glucose / HgbA1c  CMP/ Fasting Glucose and Insulin |
| Medications | Steroids, retinoids, oral contraceptives, protease inhibitors |

T4, thyroxine; TSH, thyroid-stimulating hormone; CMP, comprehensive metabolic profile; UA, urinalysis; HgbA1c, glycosylated hemoglobin.

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| **Table 2. The Prevalence and Etiology of Extreme HTG (TG > 2,000 mg/dL) in Children** | | |
| **Dallas Children’s Hospital** | **Total** | **%** |
| Study Population | 30,623 | 100% |
| Extreme HTG | 31 | 0.1% |
| **Primary Genetic Causes** |  |  |
| * Type 1 Hyperlipoproteinemia, monogenic (Familial Chylomicronemia Syndrome or FCS) | 5 | 14% |
| **Secondary Causes** |  |  |
| * Uncontrolled Diabetes | 11 | 30% |
| * L-ASP and Steroids for Acute Lymphocytic Leukemia | 10 | 28% |
| * Sirolimus/Tacrolimus Therapy after solid organ transplantation | 5 | 14% |

Data from a tertiary children’s hospital (6).

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| **Table 3. Triglyceride Levels in Children 12-19 Years of Age. NHANES data 1999 to 2008** | | | | |
| **TG Concentration** | **Normal** | **Mild-Mod** | **High** | **Missing**  **Data** |
| **Triglyceride Levels (mg/dL)** | **<150** | **150-499** | **> 500** |
| Sample (n) | 2872 | 316 | 3 | 57 |
| Weighted to US population (n) | 29,168,008 | 3,464,483 | 59,946 | 465,332 |
| Weighted % for each category | 88.0% | 10.5% | 0.2% | 1.4% |

NHANES, National Health and Nutrition Examination Survey (7)

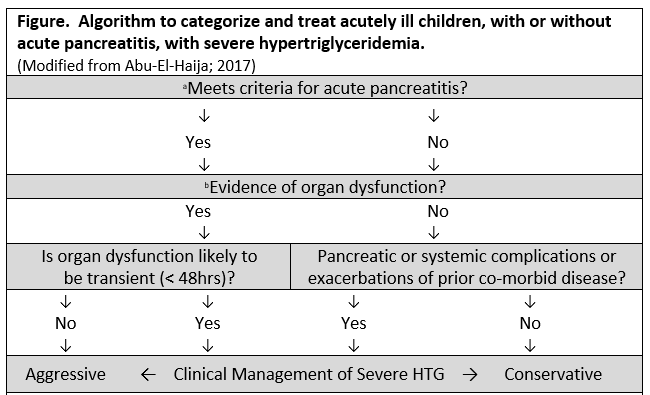
## PANCREATITIS

One of the main concerns in children with SHTG is the development of acute pancreatitis (AP). When present AP is associated with significant morbidity and can be life-threatening. Although SHTG is a rare cause of AP in children, depending upon the etiology, it may be recurrent. TG-associated AP typically occurs in individuals with a pre-existing lipid abnormality, such as a monogenic disorders of TG metabolism (Familial Chylomicronemia Syndrome) or those with one or more secondary risk factors (e.g., poorly controlled diabetes, alcohol use, or use of a medication that can provoke SHTG) in combination with small-effect genetic variants leading to HTG (Multifactorial Chylomicronemia Syndrome). Compared to other causes, SHTG-related AP is associated with increased severity and mortality, higher frequencies of co-morbidities and systemic complications, longer length of hospitalization, and more frequent recurrence (8). In general, it is believed that a TG level of 1,000 mg/dl or more is needed to precipitate an episode of AP.

AP in children has been defined as having the presence of at least 2 of the following 3 criteria (9):

1. Abdominal pain compatible with pancreatic origin;
2. Amylase and/or lipase at least 3 times upper limits of normal; and
3. Imaging suggestive of or compatible with pancreatic inflammation.

Not all children with AP have abnormal levels of serum amylase and/or lipase. Furthermore, interference with colorimetric reading assays may cause falsely normal results when TG levels are greater than 500 mg/dL. A reasonable estimate of the amylase/lipase levels may be obtained with serial dilutions of the serum. Compared to amylase, serum lipase appears to have higher specificity and sensitivity for AP. To assist in clinical-decision making, Abu-El-Haija published guidelines to help categorize the severity of children with AP (10). Categorization may be a helpful clinical tool in determining how aggressively to treat SHTG in this setting. We have modified this guideline to aid clinicians in determining the potential benefit of aggressive TG management of hospitalized children with SHTG who are critically ill, with or without pancreatitis. (Figure)



**Figure. Algorithm to categorize and treat acutely ill hospitalized children, with or without acute pancreatitis, with SHTG (10).**

aPresence of at least 2 of the following 3 criteria: 1) abdominal pain compatible with pancreatic origin; 2) amylase and/or lipase at least 3 X ULN; and 3) imaging suggestive of/compatible with pancreatic inflammation (9); bCriteria of organ dysfunction as per the International Pediatric Sepsis Consensus (modified from 11).

1. Cardiovascular Dysfunction
   1. One or more of the following despite administration of isotopic IV fluid bolus > 40 mL/kg in 1 hr.
      1. Hypotension - Decrease in BP < 5th% for age or systolic BP < 2 SD below normal for age.
      2. Need for vasoactive drug to maintain BP in normal range (dopamine > 5 mcg/kg-1/mL-1 or dobutamine, epinephrine, or norepinephrine at any dose).
   2. Two of the following:
      1. Unexplained metabolic acidosis (BD > 5 mEq/L).
      2. Increased arterial lactate > 2 X ULN.
      3. Oliguria: urine output < 0.5 mL/kg-1/hr-1.
      4. Core to peripheral temperature gap > 3° C.
2. Respiratory Dysfunction
   1. One or more of the following in absence of pre-existing lung disease or cyanotic heart disease.
   2. PaO2/FIO2 < 300 in absence of cyanotic heart disease or pre-existing lung disease.
   3. PaCO2 > 65 torr or 20 mmHg over baseline PaCO2.
   4. Proven need or > 50% FIO2 to maintain saturation > 92%.
   5. Need for non-elective mechanical ventilation.
3. Renal Dysfunction
   1. Serum creatinine ≥ 2 X ULN for age; or
   2. 2-fold increase in baseline creatinine.

BD = base deficit; BP = blood pressure; SD = standard deviation; ULN = upper limit of normal.

## TREATMENT OF HTG-RELATED PANCREATITIS

The management of acute pancreatitis secondary to HTG is similar to the management of pancreatitis due to other causes (Table 4) except for the need to lower TG levels as quickly as possible. With cessation of food intake plasma TG usually decrease rapidly (approximately 50% decrease in 24 hours). Parenteral feeding with lipid emulsions should be avoided since they will delay the clearance of TG rich lipoproteins and exacerbate the HTG. In patients on ventilators the use of propofol should be avoided. Reduction of TG levels to well below 1,000 mg/dL generally prevents further episodes of pancreatitis.

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| **Table 4. Guidelines for Treatment of Children with Acute Pancreatitis**  (Modified from 12) |
| * Adequate fluid resuscitation with crystalloid appears key, especially within the first 24 hours. * Analgesia may include opioid medications when opioid-sparing measures are inadequate. * Pulmonary, cardiovascular, and renal status should be closely monitored, particularly within the first 48 hours. * Enteral nutrition should be started as early as tolerated, whether through oral, gastric, or jejunal route. Lipid emulsions should not be used. * There is little evidence to support the use of prophylactic antibiotics, antioxidants, probiotics, or protease inhibitors. * Esophagogastroduodenoscopy, endoscopic retrograde cholangiopancreatography, and endoscopic ultrasonography have limited roles in diagnosis and management. * Children should be carefully followed for development of early or late complications and recurrent attacks. | |

## TREATMENT OF SEVERE HYPERTRIGLYCERIDEMIA IN PATIENTS WITH PANCREATITIS

Children with SHTG who are symptomatic, especially those with severe pancreatitis, may require rapid TG lowering. In situations where urgent reduction in TG levels is needed, a more aggressive approach than fasting and avoidance of fat may be indicated, including use of intravenous insulin, heparin, or both (13), and TG removal (e.g., plasmapheresis, apheresis) (Table 5). A single session of plasmapheresis has been shown to lower TG levels by up to 70% (14). While apheresis can rapidly lower TG, rigorous proof of efficacy is lacking. Studies comparing technical aspects of apheresis are also limited, such as different apheresis techniques (plasma exchange vs. double-membrane filtration) and proper fluid replacement (fresh frozen plasma vs. albumin). Apheresis is expensive, not widely available and vascular access challenging. Furthermore, a large retrospective study comparing two groups of adults with HTG before and after the availability of apheresis found no benefit (15). However, the authors suggested the timing of apheresis could be a critical factor, based on other reports showing that maximal reduction in morbidity and mortality can be achieved when apheresis is used as early as possible. Randomized trials have not compared the efficacy of insulin and heparin to standard therapy or apheresis for the treatment of pancreatitis secondary to HTG. In patients with poorly controlled diabetes (i.e., elevated plasma glucose levels) insulin should be administered to both lower glucose levels and increase lipoprotein lipase activity thereby accelerating the clearance of TG rich lipoproteins.

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| **Table 5. More Aggressive Management for HTG** | | |
| **Method** | **Route** | **Mechanism** |
| aInsulin | * Dose: 0.05-0.1/kg/hr by continuous IV infusion. * Administer concomitant IV dextrose to avoid hypoglycemia. * Consider use of the “2-bag” system to titrate insulin and dextrose delivery. | * Insulin increases lipoprotein lipase (LPL) activity which can degrade chylomicrons and thus reduce serum TG. * Intravenous insulin may be more effective than subcutaneous insulin in severe cases of HTG. |
| bHeparin | * Generally, not recommended as a monotherapy. | * Stimulates release of endothelial LPL into circulation. * However, use of heparin may only result in transient rise in LPL followed by increased degradation of plasma stores causing LPL deficiency. |
| cDouble membrane filtration or plasma exchange | * Adequate vascular access may be challenging. * Expensive procedure; not available in all medical centers. | * The beneficial effect of plasmapheresis is believed to be due to a rapid decrease in TG levels. * The effects of heparin, the removal of excessive proteases from the plasma, and replacement of consumed protease-inhibitors with new ones from donor plasma may play an additional beneficial role. * Use of donor plasma carries risks of transfusion-related allergic reaction or infection. * Requires transient anti-coagulation. |

a(16), b(17), c(18).

Presently there are no pediatric guidelines to assist clinical decision-making when more aggressive therapy might be appropriate. In general, more aggressive TG-lowering should be considered in symptomatic children who fail to respond to conventional treatment (avoidance of fat intake) and in whom there is evidence of organ dysfunction or failure (Figure). In addition to the parameters listed in the Figure, given the effects of SHTG, alternated sensorium may also be considered as an indication for aggressive TG lowering. Although plasma exchange for treating TG-related AP was included in the 2007 Guidelines on the Use of Therapeutic Apheresis in Clinical Practice from the Apheresis, the strength of the evidence was assigned to category III (“suggestion of benefit or for which existing evidence is insufficient to establish or clarify the risk/benefit”) (19). Therefore, clinical judgement is needed in deciding when use of more aggressive HTG-lowering treatment.

## FOLLOW-UP CARE

Following recovery from the acute episode of pancreatitis, the goal is to maintain a TG level of 500mg/dL or less. Management of HTG is discussed in detail in other Endotext chapters (2-5) and therefore will only be briefly discussed here. It is very important to recognize that the treatment of HTG is different in individuals with familiar chylomicronemia syndrome (FCS) vs. multifactorial chylomicronemia syndrome (MCS).

The primary treatment of individuals with FCS is dietary. Dietary fat calories need to be severely restricted to approximately 5-20% of calories. Such a fat restricted diet is very difficult for most patients to follow consistently. Medium-chain triglycerides (MCT), which are not incorporated into chylomicrons and are delivered to the liver via the portal vein, are a potential alternate source of fats for these patients. One should monitor for deficiency of fat-soluble vitamins (A, D, E, K) and recommend appropriate replacement as needed. Pregnancy in adolescents with FCS need to be carefully planned with close monitoring to avoid acute pancreatitis. Similar, to the treatment of MCS described below, drugs that increase TG levels should be discontinued if possible and medical conditions that tend to increase TG levels, optimally treated. Omega-3-fatty acids (fish oils) do not usually lower TG levels in patients with FCS. Fibrates are also not effective; however, a few studies have suggested that orlistat may be beneficial. Volanesorsen (Waylivra ®), an antisense oligonucleotide inhibitor of apolipoprotein C-III mRNA, is approved for treatment of FCS in Europe but not the United States. FCS patients treated with volanesorsen had a 77% decrease at 3 months in TG levels (mean decrease of 1,712 mg/dl) whereas those receiving placebo had an 18% increase in TG levels (20). Volanesorsen can lead to thrombocytopenia and, therefore, was not approved in the US but it is hoped that second generation inhibitors of apolipoprotein C-III will not demonstrate this side effect.

In patients with MCS, it is important to reverse the secondary factors that result in the marked HTG. For example, improving diabetic control, weight loss, eliminating ethanol intake, and discontinuing drugs that raise TG levels. In patients with markedly elevated TG levels (>1000mg/dL) initial management should include a very low-fat diet until the TG levels decrease. Once the TG decreases, a diet that reduces carbohydrate intake, particularly simple sugars, and minimizes alcohol intake should be encouraged. Weight loss can be helpful in lowering TG levels in those who are overweight or obese. If TG remain elevated after the above measures one can consider the use of drugs that lower TG levels such as omega-3-fatty acids and fibrates (Table 6). Many patients with MCS are at high risk for the future development of atherosclerotic cardiovascular disease. Therefore, once the high TG levels are lowered a repeat lipid panel is recommended to determine whether treatment strategies to reduce the risk of ASCVD are needed.

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| **Table 6. Medications for Primarily Lowering Triglycerides** (21) | | | | |
| **Medication** | **Pediatric Dosing** | **Adult Dosing** | **Side Effects** | **Indication / Comments** |
| **Fibric Acid Derivatives** | | | | |
| Fenofibrate  (Many generic preparations available) | Pediatric safety and efficacy not established. Not FDA approved for use in children. | Product specific. Generally, employ full dose in the setting of normal renal function. | Skin rash, gastrointestinal (nausea, bloating, cramping), myalgia; lowers blood cyclosporine levels; potentially nephrotoxic in cyclosporine treated patients. Avoid in patients with CrCl < 30 mL/min. | Hypertriglyceridemia.  Monitor renal function; avoid in the presence of severe renal function. Regular monitoring of liver function test is required. Discontinue if persistent elevation of LFTs > 3 X ULN. |
| Gemfibrozil  (Lopid) | Pediatric safety and efficacy not established. Not FDA approved for use in children. | 1200 mg p.o. daily, divided BID, 30 mins before breakfast and dinner | Potentiates warfarin action. Absorption of gemfibrozil diminished by bile acid sequestrants. | Hypertriglyceridemia.  Use with caution in patients with renal impairment, contraindicated with severe renal impairment; use contraindicated with hepatic impairment. Avoid with concurrent statin therapy. |
| **Nicotinic Acid** | | | | |
| Niacin  (Multiple preparations available) | Age ≥ 10  Pediatric safety and efficacy not established. Not FDA approved for use in children. If used, suggested dose  Initial: 100-250 mg/d (Max: 10 mg/kg/day) divided three times daily with meals | Slowly titrate to max dose of intermediate release niacin (3 g/day) or slow-release niacin) 2 g/day) | Prostaglandin-mediated cutaneous flushing, headache, warm sensation, and pruritus; dry skin; nausea; vomiting; diarrhea; and myositis. | Adjunct therapy to reduce high TG.  For Ped dosing may titrate weekly by 100 mg/day or every 2 – 3 weeks by 250 mg/day. No dosing adjustment has been provided by the manufacturer for renal or hepatic impairment. Contraindicated in the presence of significant unexplained hepatic dysfunction, active liver disease, or unexplained persistent LFT elevation. |
| **Omega 3 Fatty Acids** | | | | |
| Ethyl esters  (Lovaza) | Pediatric safety and efficacy not established. Not FDA approved for use in children. | 2-4 g EPA + DHA daily, divided BID | Eructation, dyspepsia. Diarrhea (7%-15%) most commonly reported. May enhance anticoagulant and antiplatelet effects of other medications. | Adjunct therapy to reduce high TG.  No dosage adjustments required for impaired renal or hepatic function. Periodic monitoring of ALT and AST is recommended for patients with hepatic impairment. |
| Icosapent  (Vascepa) | Pediatric safety and efficacy not established. Not FDA approved for use in children. | 2-4 g EPA daily, divided BID | Arthralgia, oropharyngeal pain |
| **Statins** | | | | |
| Statins (Multiple preparations available) | Not FDA approved for use in children other than familial hypercholesterolemia. | Product specific. | Headache; nausea; sleep disturbance; elevations in hepatocellular enzymes and alkaline phosphatase. Myositis and rhabdomyolysis, primarily when given with gemfibrozil or cyclosporine; myositis is also seen with severe renal insufficiency (CrCl < 30 mL/min). | If used off label in HTG, statins are most often used in combination with other drugs, such as fibrates, in order to achieve synergistic effects. |

## CONCLUSION

Aggressive therapy in symptomatic children with SHTG, when indicated, can rapidly lower levels of TG, potentially reducing morbidity and mortality in critically ill hospitalized children with and without acute pancreatitis. An algorithm to categorize severity of illness, the presence of pancreatitis and/or organ dysfunction, and local pancreatic or systemic complications or exacerbations of prior co-morbid disease can assist clinical decision-making in helping to determine appropriate candidates for aggressive TG-lowering therapy.

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