

A CLINICAL APPROACH TO AGGRESSIVE TREATMENT OF CHILDREN WITH SEVERE HYPERTRIGLYCERIDEMIA

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ABSTRACT

Severe hypertriglyceridemia (SHTG) is uncommon in children. Those with triglyceride (TG) levels of 1,000 mg/dL or more are likely to have an underlying monogenic or polygenic disorder affecting TG metabolism. SHTG may also occur in youth who are obese and insulin resistant, those with poorly controlled diabetes, or who require medications that interfere with TG metabolism, especially in those with an underlying genetic predisposition. 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 treatment of hypertriglyceridemia in children. Presently, however, there are no pediatric guidelines to assist clinical decision-making when aggressive therapy of SHTG might be indicated. In this chapter we review the mechanisms associated with SHTG, discuss management, follow-up, and outcomes, and

suggest an approach for use of aggressive TG-lowering therapy.

INTRODUCTION

Severe hypertriglyceridemia 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, individuals with monogenic disorders have serve elevations of TG, typically 1000 mg/dL or more, while those with polygenic and small-effect genetic variants that contribute to alterations in lipid and lipoprotein metabolism, particularly with secondary causes, are more common (Table 2). Such severe elevations may cause significant morbidity which occasionally may be life-threatening, necessitating aggressive TG lowering.

Table 1. Common Secondary Causes of Dyslipidemia

Condition	Screening Tests
Hypothyroidism	Free T4, TSH
Liver Diseases	CMP
Kidney diseases	CMP / UA
Diabetes Mellitus	CMP / UA / fasting or random glucose / HbA1c
Obesity / Insulin Resistance	CMP / fasting glucose and insulin
Medications	Steroids, retinoids, oral contraceptives, protease inhibitors

Free T4-free thyroxine; TSH-thyroid-stimulating hormone; UA-urinalysis; CMP-Comprehensive Metabolic Profile; HbA1c-hemoglobin A1c

Table 2. Estimated Prevalence of Severe Hypertriglyceridemia. The Copenhagen General Population Study. Modified from (15)

Subjects: >70,000 Adults Age: >20 years			Polygenic* and Small-Effect Variants	Can be Monogenic**
% Pop	26%	46%	28%	0.1%
TG (mg/dL)	<88	88-177	177-797	797-1329
Severity			<----- Mild to High ----->	<----- Severe ----->
Primary Health Risk			Increase in premature CVD	Chylomicronemia, Pancreatitis, CVD Risk Less Likely
*LPL, APOA5, GCKR, APOB, LMF1, GPIHBP1, CREBH1, APOC2, APOE				
**LPL, APOC2, APOA5, LMF1, GPIHBP1 AND GPD1				

PANCREATITIS

One of the main concerns in individuals with SHTG is the development of acute pancreatitis (AP). When present AP is associated with significant morbidity which can be life-threatening. Although SHTG is a rare cause of AP in children, depending upon etiology it may be recurrent. TG-associated AP typically occurs in individuals with a pre-existing lipid abnormality, such as a monogenic disorder of TG metabolism, in those with one or more secondary risk factors (e.g., poorly controlled diabetes, alcohol use, or use of a medication that can provoke SHTG), or a combination of both. Compared to other causes, SHTG-related AP may contribute to increased severity and mortality, higher frequencies of co-morbidities and systemic complications, longer length of hospitalization and more frequent recurrence (1). 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 the presence of at least 2 of the following 3 criteria (2): 1) abdominal pain compatible with pancreatic origin; 2) an amylase and/or lipase level at least 3 times the upper limits of normal (ULN); 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 assays that use colorimetric methods may cause falsely normal results when TG levels are greater than 500 mg/dL. In these circumstances, an estimate of the amylase/lipase levels can be obtained following 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 (3) to help categorize the severity of children with AP (Figure 1). Categorization may be a helpful clinical tool in determining how aggressively to treat SHTG in this setting.

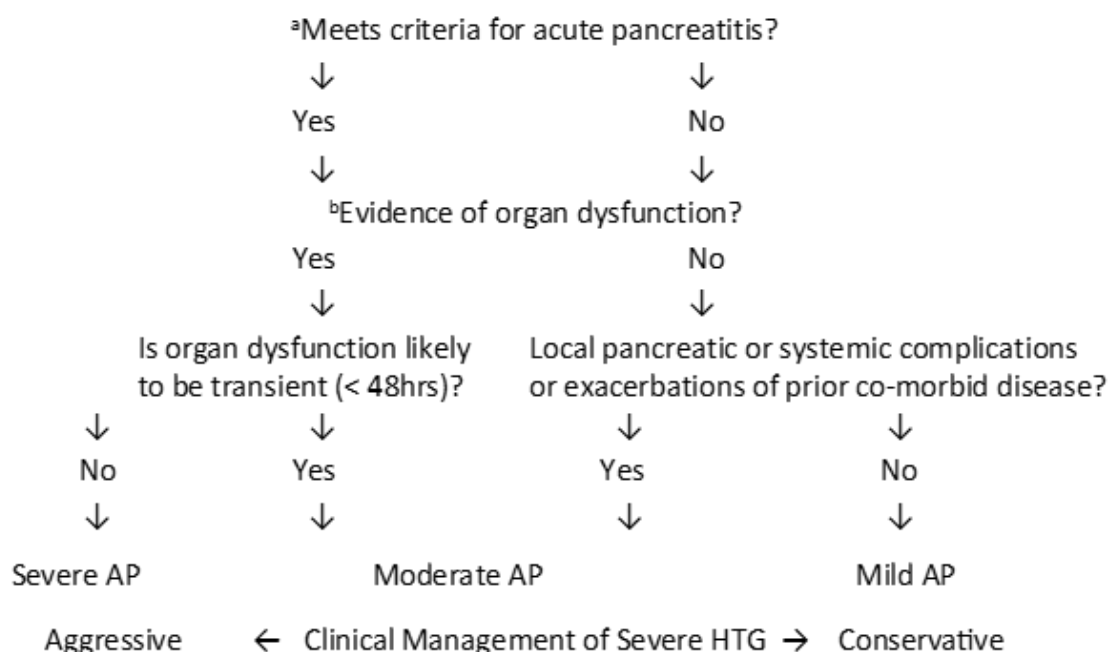


Figure 1. Algorithm to categorize severity of pediatric acute pancreatitis (AP) and recommended treatment of HTG. Modified from (3).

^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. (2)

^bCriteria of organ dysfunction as per the International Pediatric Sepsis Consensus [Modified from (16)].

I. Cardiovascular Dysfunction

a. One or more of the following despite administration of isotonic IV fluid bolus > 40 mL/kg in 1 hr.

- Hypotension - Decrease in BP < 5th% for age or systolic BP < 2 SD below normal for age.
- 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).

b. Two of the following:

- Unexplained metabolic acidosis (Base Deficit > 5 mEq/L).
- Increased arterial lactate > 2 X ULN.
- Oliguria: urine output < 0.5 mL/kg⁻¹/hr⁻¹.
- Core to peripheral temperature gap > 3° C.

II. Respiratory Dysfunction

a. One or more of the following in absence of pre-existing lung disease or cyanotic heart disease.

- PaO₂/FIO₂ < 300 in absence of cyanotic heart disease or pre-existing lung disease.
- PaCO₂ > 65 torr or 20 mmHg over baseline PaCO₂.
- Proven need or > 50% FIO₂ to maintain saturation > 92%.
- Need for non-elective mechanical ventilation.

III. Renal Dysfunction

- Serum creatinine ≥ 2 X ULN for age; or
- 2-fold increase in baseline creatinine.

TREATMENT OF HYPERTRIGLYCERIDE-RELATED PANCREATITIS

Treatment of Acute Pancreatitis

The clinical course and treatment of SHTG-related AP in children is generally no different from that of pancreatitis of other causes (Table 3). Reduction of TG levels to well below 1,000 mg/dL generally prevents further episodes of pancreatitis.

Table 3. Guidelines for Treatment of Children with Acute Pancreatitis. Modified from (17).

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.
 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.

Once placed NPO, patients with AP generally experience a rapid decline in TG levels, at which time a very low-fat diet can be initiated. In situations where urgent reduction in TG levels is needed, a more aggressive approach may be indicated, including use of intravenous insulin, heparin, or both (4), and TG removal (e.g., plasmapheresis, apheresis) (Table 4). A single session of plasmapheresis has been shown to lower TG levels by up to 70% (5). 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 and not widely available. Furthermore, a large retrospective study comparing two groups of adults with HTG before and after the availability of apheresis found no benefit (6). 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. Comparable studies in children are not available. Randomized trials have not compared the efficacy of insulin and heparin to apheresis for the treatment of HTGP.

Table 4. More Aggressive Management for Hypertriglyceridemia (18,19,20)

Method	Route	Mechanism
Insulin	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 triglycerides. Intravenous insulin may be more effective than subcutaneous insulin in severe cases of HTG.
Heparin	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.

Double 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.
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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 those who fail to response to conventional treatment and in whom there is evidence of organ dysfunction or failure (Figure 1). In addition to the parameters listed in Figure 1, given the effects of SHTG, alternated sensorium may also be 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") (7). Therefore, clinical judgement is needed in deciding when to use of more aggressive HTG-lowering treatment.

Prevention of Future Episodes of Acute Pancreatitis

Although lipid lowering drugs, mainly fibric acid derivatives and omega-3-fatty acids, have been shown to effectively lower TG in adults, none are FDA approved for use in children (Table 5). Published guidelines, however, suggest lipid lowering drugs should be considered in children 18 years of age or younger with persistent TG \geq 500 mg/dL (8, 9).

Table 5. Medications for Primarily Lowering Triglycerides [Modified from (9).

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 > 3X 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 pediatric 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				
Multiple preparations available	Not FDA approved for use in children other than familial hypercholesterolemia.	Product specific.	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.

Fenofibrate, a potent hypolipemic agent, is widely used in patients with hypertriglyceridemia. A moderate reversible increase in serum creatinine is a well described side effect of fenofibrate therapy, although the mechanism remains unknown (10). It does not appear to reflect an impairment of renal function, nor an alteration of tubular creatinine secretion, and is not falsely increased by dosage interference. Furthermore, a fenofibrate-induced increase

of daily creatinine production is not readily explained by accelerated muscular cell lysis. Rather, it has been proposed that fenofibrate increases the metabolic production rate of creatinine (10). Although current evidence does not suggest fenofibrate is nephrotoxic, close monitoring of serum creatinine is recommended, especially in high-risk patients. Increases in serum creatinine levels ≥ 30% may suggest the need for discontinuation (11).

While over-the-counter long chain omega-3-fatty acids have variable TG-lowering effects, prescription preparations lower TG levels by 20-50%. In lipoprotein lipase deficiency states, omega-3-fatty acids may aggravate severe HTG (12).

Use of niacin, which lowers TGs 10-30%, increases HDL-C by 10-40%, and lowers LDL-C by 5-20%, is limited by common side effects, such as flushing and pruritus. In addition, it may contribute to insulin resistance, further increasing TG levels. Bile acid sequestrants may worsen HTG and are contraindicated in patients with SHTG (> 1000 mg/dL).

Several novel therapies for treatment of HTG are in development, but their clinical efficacy, cost-effectiveness, and indications, especially in children, have not yet been established.

Following recovery from the acute episode of pancreatitis, patient should be encouraged to adopt a healthy lifestyle, including a diet low in saturated fat and cholesterol, avoiding excessive carbohydrate intake, avoidance/cessation of smoking, and 30-60 minutes of moderate-to-vigorous daily physical activity. In selected cases, pharmacotherapy has

been recommended to prevent pancreatitis and/or reduce risk of cardiovascular disease, although outcome data are lacking. Youth at-risk of recurrent episodes of HTG-related pancreatitis should also be encouraged to avoid use of alcohol, other medications associated with HTG, such as isotretinoin, and in girls, oral contraceptives. Tests for genetic mutations associated with pancreatitis may be informative (13, 14).

CONCLUSION

Aggressive TG-lowering therapy, when indicated, can rapidly lower severely elevated levels of triglycerides, potentially reducing morbidity and mortality associated with TG-related acute pancreatitis. An algorithm to categorize severity of acute pancreatitis, the presence of organ dysfunction or failure, 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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