Very Severe Hypertriglyceridemia (TGL ≥ 1000 mg/dL): Management - Adult - Inpatient/Emergency Department - Clinical Practice Guideline

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Introduction
Hypertriglyceridemia is a common dyslipidemia that has many causes.\(^1\) It is associated with increased atherosclerotic cardiovascular disease (ASCVD) risk that often coexists with other lipoprotein abnormalities.\(^2\) Mild and moderate hypertriglyceridemia places individuals at increased ASCVD risk, but severe and very severe hypertriglyceridemia places individuals at additional risk of pancreatitis and chylomicronemia syndrome.\(^3\) This guideline outlines treatment of severe-very severe hypertriglyceridemia. “Very severe” is defined for the focus of this guideline and to answer the clinical questions outlined below. For management of mild-moderate, or severe hypertriglyceridemia, refer to the UW Health Hyperlipidemia: Management – Adult – Inpatient/Ambulatory clinical practice guideline for ASCVD risk reduction.

Scope
Intended User(s): Physicians, Advanced Practice Providers, Registered Nurses, Pharmacists

Objective(s): To provide guidance on treatment of very severe hypertriglyceridemia for patients seen in the emergency room, urgent care, or who are admitted.

Target Population: Adult patients (age $\geq 18$ years) with very severe hypertriglyceridemia (triglycerides $\geq 1000$ mg/dL.)

Clinical Questions Considered:
- Which patients with very high triglycerides should be admitted for inpatient care?
- What are the initial diagnostic strategies for patients with very severe hypertriglyceridemia?
- What are the treatment options for patients with very severe hypertriglyceridemia?
- When is plasmapheresis indicated for patients with hypertriglyceridemia?

Definitions

Table 1. Categories of Triglycerides Elevations\(^3-5\)

<table>
<thead>
<tr>
<th>Category</th>
<th>Triglycerides (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>$&lt; 150$</td>
</tr>
<tr>
<td>Mild</td>
<td>150-199</td>
</tr>
<tr>
<td>Moderate</td>
<td>200-499</td>
</tr>
<tr>
<td>Severe</td>
<td>500-999</td>
</tr>
<tr>
<td>Very severe</td>
<td>$\geq 1000$</td>
</tr>
</tbody>
</table>

Causes of Hypertriglyceridemia
Hypertriglyceridemia can be primary or secondary (i.e., due to other conditions and treatments. See Table 2)\(^1\) Triglycerides are generally measured in the fasting state and can be divided into categories: normal, mild, moderate and severe elevations (see Table 1). Hypertriglyceridemia can result from increased triglycerides production, decreased catabolism, or a combination of both.\(^3\) Almost all patients with very severe elevations in triglycerides have primary and secondary contributors.\(^1\)
Table 2. Causes of Hypertriglyceridemia

<table>
<thead>
<tr>
<th>Primary Causes</th>
<th>Secondary Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial combined hyperlipidemia</td>
<td>Untreated/poorly controlled diabetes mellitus</td>
</tr>
<tr>
<td>Lipoprotein lipase deficiency</td>
<td>Obesity</td>
</tr>
<tr>
<td>Familial dysbetalipoproteinemia</td>
<td>High fat/high carbohydrate/high caloric diet</td>
</tr>
<tr>
<td>Apolipoprotein CII deficiency</td>
<td>Excessive alcohol consumption</td>
</tr>
<tr>
<td>Apolipoprotein C-III excess</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Familial chylomicronemia syndrome</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td></td>
<td>Pregnancy</td>
</tr>
<tr>
<td></td>
<td>Medications (see Table 3)</td>
</tr>
</tbody>
</table>

Metabolism

In the exogenous pathway, dietary triglycerides (fats) are assembled in the intestinal wall into chylomicrons which enter the venous circulation. Through interactions with lipoprotein lipase on the luminal surface of the capillary endothelial cells, triglycerides in the core of the chylomicrons are hydrolyzed into free fatty acids and glycerol which can be used as energy sources or for gluconeogenesis. In the endogenous pathway, triglycerides produced by the liver are carried by very low-density lipoproteins (VLDL) and are also catabolized by lipoprotein lipase. The plasma triglycerides level reflects the concentration of triglyceride-carrying lipoproteins (mainly VLDL and chylomicrons). In severe and very severe hypertriglyceridemia, the lipoprotein lipase catabolism system is saturated. Thus after a fatty meal, when a patient's level is already above 1000 mg/dL, the triglycerides level can significantly increase.

Clinical Presentation

Severe and very severe hypertriglyceridemia may result in hyper-viscous serum and a clinical condition called "chylomicron syndrome" which manifests as acute pancreatitis, abdominal pain, impaired cognition/memory, paresthesias, and hepatosplenomegaly. Hypertriglyceridemia-induced pancreatitis was the third leading cause of pancreatitis (~10% of cases) in a population based study. Assessment of the patient who presents with severe/very severe triglycerides elevation includes a careful medical history, clinical exam, laboratory assessment, and evidence chylomicron syndrome symptoms (e.g., paresthesias, abdominal pain.) Because there is no specific triglycerides level that will always result in chylomicron syndrome manifestation, a careful medical history must be part of the clinical assessment.

When the serum triglycerides level exceeds 1000 mg/dL, typical physical exam findings can be found. Eruptive xanthomas are skin manifestations of very severe triglycerides elevations due to trapping of triglycerides in cutaneous histiocytes. Eruptive xanthomas are yellow papules on an erythematous base found on the extensor surfaces of the extremities and on the buttocks. In addition, those with type III hyperlipoproteinemia can have striate xanthomata of the palms and tuberoeruptive xanthoma. When triglycerides are high, the serum can have a milky supernatant indicating the presence of chylomicrons. Lipemia retinalis (pallor of the optic fundus where the retinal veins and arteries appear white or creamy) also may be present.
Recommendations

Clinical Assessment
The medical history should focus on assessment of symptoms (see Figure 1, Pathway Diagram). These symptoms can be as overt as acute pancreatitis and/or as non-specific as abdominal pain, nausea/vomiting, vision changes, impaired cognition, or paresthesias. A thorough search for contributing medications (see Table 3) or secondary conditions (see Table 2) should be performed. Laboratory data such as a serum glucose, hemoglobin A1C, creatinine, thyroid stimulating hormone, urinalysis with protein: creatinine ratio should be obtained in patients that present with severe/very severe hypertriglyceridemia (UW Health Low quality of evidence, C recommendation). Please note that these triglyceride-rich lipoproteins may also result in falsely low amylase levels and pseudohyponatremia. In one study, serum amylase was near-normal in 50% of patients presenting with hypertriglyceridemia-induced pancreatitis, therefore if clinical suspicion remains elevated, appropriate imaging may need to be obtained.

Table 3. Common drugs/medication that can increase triglycerides

| • Beta-blockers          | • Alcohol          |
| • Glucocorticoids       | • Protease inhibitors |
| • Estrogens             | • Tacrolimus       |
| • Progestins            | • Cyclosporine     |
| • Tamoxifen             | • Clozapine        |
| • Androgenic steroids   | • Atypical antipsychotics (e.g., olanzapine) |
| • Retinoids, isotretinoin | • Valproate       |
| • Thiazide/thiazide-type diuretics | **Other medications also may contribute |
| • Loop diuretics        |                      |

Acute management of very severe hypertriglyceridemia
Acute management of very severe hypertriglyceridemia (>1000 mg/dL) is based on symptoms. If the patient has pancreatitis or hyperviscosity symptoms such as abdominal pain, nausea/vomiting, vision changes, impaired cognition or paresthesias, the patient should be admitted to the hospital for more definitive treatment. If the patient is asymptomatic, then secondary or reversible causes should be addressed based on initial laboratory and clinical work-up.

Fenofibrate (160 mg/day) or micronized fenofibrate (200 mg/day) should be started if therapy is not contraindicated, patient’s creatinine clearance >30 ml/min, and liver enzymes are acceptable (i.e., AST/ALT <2.5x ULN). (UW Health Low quality of evidence, C recommendation) Heparin is not routinely recommended for treatment of severe hypertriglyceridemia due to bleeding risk, especially if the patient has pancreatitis, unless there is a strong indication for use (e.g., pulmonary embolism, deep vein thrombosis, etc.). (UW Health Low quality of evidence, C recommendation)

The patient will need close follow-up appointments and it is suggested to follow-up with a primary care physician within 2 weeks and preventive cardiology within 6 weeks. (UW Health Very low quality of evidence, C recommendation). Patient should not be discharged until the serum triglycerides are under 500 mg/dL and patient is clinically stable (UW Health Very low quality of evidence, C recommendation).
Symptomatic Patient with Very Severe Hypertriglyceridemia

The patient with symptomatic hypertriglyceridemia should be admitted to the hospital and be made N.P.O. to allow for clearance of chylomicrons.³ (UW Health Low quality of evidence, C recommendation) Secondary causes should be identified and addressed. Offending medications should be stopped. A nutrition consult should be placed for all patients with very severe hypertriglyceridemia.³ (UW Health Low quality of evidence, C recommendation) Once the serum triglycerides are <1000 mg/dL, the patient should be started on a very low-fat diet (< 15% of calories), calorically appropriate diet. (UW Health Low quality of evidence, C recommendation)

Hyperglycemia should be addressed through glycemic control (e.g., metformin, insulin infusion, diabetes management consultation) and triglycerides-lowering pharmacotherapy should be started. In the setting of concurrent hyperglycemia with hypertriglyceridemia, intravenous insulin may be considered for glucose and triglycerides control.¹⁴,¹⁵ (UW Health Low quality of evidence, C recommendation)

Fibrates are the first line treatment of hypertriglyceridemia if not contraindicated. If creatinine clearance is >30 ml/min, and AST/ALT <2.5x ULN, fenofibrate (160 mg/day) or micronized fenofibrate (200 mg/day) should be started.³,¹² (UW Health Low quality of evidence, C recommendation) In general, niacin is not used.³ Statins and high dose omega-3 fatty acid containing fish oil capsules are adjunctive therapies once triglycerides are <1000 mg/dL.¹¹,¹⁶ (UW Health Low quality of evidence, C recommendation) For patients without pancreatitis, once diet is tolerated and symptoms resolve, the patient should be scheduled for close follow up with the primary care provider (2 weeks) and preventive cardiology (6 weeks). (UW Health Low quality of evidence, C recommendation)

Plasmapheresis

In patients with hypertriglyceridemia-induced pancreatitis or severe hyperviscosity symptoms, plasmapheresis can lower triglycerides and lead to symptom resolution more quickly than standard medical care; it also can reduce length of stay.¹²,¹⁸ However, the effects of therapeutic plasmapheresis for hypertriglyceridemia-induced pancreatitis on clinical outcomes have not been demonstrated in randomized clinical trials.¹² In a small single center case series there was an 80% reduction in plasma triglycerides with the use of therapeutic plasma exchange, but there was no difference between early and late mortality.¹⁸ Because patients with hypertriglyceridemia-induced pancreatitis are at increased risk of mortality (up to 30% in some series)¹⁷ plasmapheresis should be considered in patients with pancreatitis, abdominal pain, or hyperviscosity symptoms. (UW Health Low quality evidence, C recommendation)

Patients receiving plasmapheresis uncommonly can have a reaction characterized by nausea, flushing, and hypotension, so the decision to perform plasmapheresis and its timing must be considered with consultation from the Pathology and Laboratory Medicine Transfusion Service.

Patients on ACE inhibitors (ACE-I) who are treated with plasmapheresis can uncommonly develop neurochemical hypotension that may be severe and life threatening. One proposed mechanism of this phenomenon is that ACE inhibitors prolong the half-life of bradykinin. The decision to perform plasmapheresis, and its timing with respect to ACE-I, must be considered in consultation with transfusion medicine physicians (see Table 5).

- ACE-inhibitors should be discontinued, when possible, for at least 24 hours prior to and until plasma exchanges have been completed.¹⁹,²⁰ (UW Health Low quality evidence, C recommendation)
• If an ACE-inhibitor has been administered within the past 24 hours, plasmapheresis usually is deferred unless the potential benefit outweighs the potential excess risk. *(UW Health Low quality evidence, C recommendation)*
  o These risks cannot be quantified so decision-making should be on a case-by-case basis, have multidisciplinary input, and should be shared with the patient so they can provide informed consent.
  o If an ACE-inhibitor has been administered within the past 24 hours, plasmapheresis must be performed in an intermediate medical care (IMC) or intensive care unit (ICU) setting.\(^{19,20}\)
• It generally is safe to defer plasmapheresis for hyperviscosity syndrome due to very severe hypertriglyceridemia if the patient has received an ACE-inhibitor in the past 24 hours. *(UW Health Low quality evidence, C recommendation)*
• For patients with abdominal pain or evidence of pancreatitis by labs or imaging, assess for signs of systemic inflammatory response syndrome (SIRS) (see Table 4). The presence of 2 or more signs of SIRS may identify patients in whom earlier plasmapheresis might be useful.\(^{21}\) *(UW Health Low quality evidence, C recommendation)*

**Table 4. Signs of SIRS\(^{21}\)**

<table>
<thead>
<tr>
<th>SIRS- defined by presence of two or more criteria:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate &gt;90 bpm</td>
<td>White blood count &lt;4,000 or &gt;12,000/mm(^3)</td>
</tr>
<tr>
<td>Core temperature &lt;36°C or &gt;38°C</td>
<td>Respirations &gt;20/min or PCO(_2) &lt;32 mm Hg(^{13})</td>
</tr>
</tbody>
</table>

**Table 5. Considerations for Plasmapheresis in Patients with Pancreatitis or Abdomen Pain Due to Very-High Triglycerides**

<table>
<thead>
<tr>
<th>ACE-I Usage</th>
<th>SIRS ≥ 2</th>
<th>SIRS = 0 or 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ACE-I taken in past 24 hours</td>
<td>Favors performing plasmapheresis</td>
<td>Consider plasmapheresis</td>
</tr>
<tr>
<td>ACE-I taken within past 24 hours*</td>
<td>Consider plasmapheresis with extra caution</td>
<td>Favors deferring plasmapheresis</td>
</tr>
</tbody>
</table>

*If plasmapheresis is performed within 24 hours of the last ACE inhibitor dose, it must be done in an IMC or ICU setting, only after multidisciplinary consultation and patient informed consent. The primary medical service may need to assist with the informed consent process.

Consult Interventional Radiology if central line placement is required. The Cardiology Consultation team and any of the Preventive Cardiology faculty are available as resources, though formal consultation is usually not necessary.

**Disclaimer**
Clinical practice guidelines assist clinicians by providing a framework for the evaluation and treatment of patients. This guideline outlines the preferred approach for most patients. It is not intended to replace a clinician’s judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.
Methodology
Development Process
Each guideline is reviewed and updated a minimum of every 3 years. All guidelines are developed using the guiding principles, standard processes, and styling outlined in the UW Health Clinical Practice Guideline Resource Guide. This includes expectations for workgroup composition and recruitment strategies, disclosure and management of conflict of interest for participating workgroup members, literature review techniques, evidence grading resources, required approval bodies, and suggestions for communication and implementation.

Methods Used to Collect the Evidence:
The following criteria were used by the guideline author(s) and workgroup members to conduct electronic database searches in the collection of evidence for review.

Literature Sources:
- Hand-searching journals, external guidelines, and conference publications

Time Period: 2017-2018

Methods to Select the Evidence:
English journals, leading medical journals, professional society publication.

Methods Used to Formulate the Recommendations:
The workgroup members agreed to adopt recommendations developed by external organizations and/or created recommendations internally via a consensus process using discussion of the literature and expert experience/opinion. If issues or controversies arose where consensus could not be reached, the topic was escalated appropriately per the guiding principles outlined in the UW Health Clinical Practice Guideline Resource Guide.

Methods Used to Assess the Quality of the Evidence/Strength of the Recommendations:
Internally developed recommendations, or those adopted from external sources without an assigned evidence grade, were evaluated by the guideline workgroup using an algorithm adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see Figure 1).
Figure 1. GRADE Methodology adapted by UW Health

Rating Scheme for the Strength of the Evidence/Recommendations:

<table>
<thead>
<tr>
<th>GRADE Ranking of Evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>We are confident that the effect in the study reflects the actual effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.</td>
</tr>
<tr>
<td>Low</td>
<td>The true effect may differ significantly from the estimate.</td>
</tr>
<tr>
<td>Very Low</td>
<td>The true effect is likely to be substantially different from the estimated effect.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GRADE Ratings for Recommendations For or Against Practice</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong (S)</td>
<td>Generally should be performed (i.e., the net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.)</td>
</tr>
<tr>
<td>Conditional (C)</td>
<td>May be reasonable to perform (i.e., may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.)</td>
</tr>
</tbody>
</table>

Recognition of Potential Health Care Disparities: None identified.
Collateral Tools & Resources
The following collateral tool and resource support staff execution and performance of the evidence-based guideline recommendations in everyday clinical practice.

Metrics
- # of patients admitted with very severe hypertriglyceridemia
- # of ER visits with very severe hypertriglyceridemia

Related Guidelines
Preventive Health Care – Adult/Pediatric – Ambulatory
Hyperlipidemia: Management – Adult – Inpatient/Ambulatory

Patient Resources
1. HFFY #519: Food Guidelines to Reduce LDL Cholesterol and Triglycerides
2. HFFY #5419: Heart Healthy Living for Women
3. HFFY #5668: A Health Guide for Women 50 or Older
4. HFFY #5669: A Health Guide for Men 50 or Older
5. HFFY #6196: Improving Your Lipid (Cholesterol) Level
6. HFFY #6419: A Health Guide for Men 50 or Older
7. HFFY #7466: Familial Hypercholesterolemia (FH) in Children
8. HFFY #7617: My Child’s Lipoprotein (a) Level
9. HFFY #7739: Your Risk of Heart and Vascular Disease
10. HFFY #7979 Getting Ready for your Fasting Blood Draw
11. Healthwise: Cholesterol and Triglycerides Tests
14. Healthwise: Well Visit: 18 to 50 Years
15. Healthwise: Well Visit: 50 to 65 Year Men
16. Healthwise: Well Visit: 50 to 65 Year Women
17. Healthwise: Well Visit: Over 65 Years
18. Health Information: Cholesterol in Children and Teens
19. Health Information: Lipid Panel

Smartset
Hyperlipidemia [87]

Protocols
Laboratory Screening and Chronic Disease Monitoring Laboratory Test Ordering in Primary Care – Adult/Pediatric – Ambulatory [93]
Primary Care Lipid Management for Prevention of Atherosclerotic Cardiovascular Disease – Adult – Ambulatory [163]
Appendix A. Management of Very Severe Hypertriglyceridemia Algorithm

**Primary and Secondary Causes of Hypertriglyceridemia**

**Primary Causes**
- Familial combined hyperlipidemia
- Lipoprotein lipase deficiency
- Familial dysbetalipoproteinemia
- Apolipoprotein C-II deficiency
- Apolipoprotein C-III excess
- Familial chylomicronemia syndrome

**Secondary Causes**
- Untreated/poorly controlled diabetes mellitus
- Obesity
- High fat/high carbohydrate/high caloric diet
- Excessive alcohol consumption
- Hypothyroidism
- Nephrotic syndrome
- Pregnancy
- Medications (see table below)

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**Common drugs/medications that can raise triglycerides**

- β-blockers
- Glucocorticoids
- Estrogens
- Progestins
- Tamoxifen
- Androgenic steroids
- Retinoids, isotretinoin
- Protease inhibitors
- Thiazide/thiazide-type diuretics
- Loop diuretics
- Tacrolimus
- Cyclosporine
- Clozapine
- Isotretinoin
- Protease inhibitors
- Atypical antipsychotics (e.g., olanzapine)
- Valproate
- Alcohol

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**Consideration for Plasmapheresis if ACE-I Usage**

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**Patient has Hypertriglyceridemia (TG ≥ 1000 mg/dL)**

- Evaluate for Primary and Secondary Causes
- Obtain Labs: Serum glucose, hemoglobin A1C, Creatinine, TSH, UA with protein/creatinine ratio

**Does patient have symptoms?**

- [i.e., abdominal pain, nausea/vomiting, vision changes, impaired cognition, paresthesias]

**Admit Patient and Treat**

- Address secondary causes
- Start fenofibrate (160 mg) or micronized fenofibrate (200 mg) daily
- Obtain diabetes management consultation if hyperglycemic
- Start glycemic control (e.g., metformin, insulin infusion) if hyperglycemic
- Patient should be NPO
- Obtain nutrition consult for very-low fat diet

**Arrange Follow-up and Discharge Patient**

- Follow-up with PCP within 2 weeks
- Follow-up with Preventive Cardiology in 6 weeks

**Consider Plasmapheresis**

- Consult Pathology/Transfusion Service for plasmapheresis
- Consult Interventional Radiology for line placement
References