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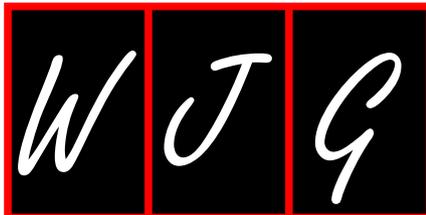
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## Case of familial hyperlipoproteinemia type III hypertriglyceridemia induced acute pancreatitis: Role for outpatient apheresis maintenance therapy

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### Abstract

Hypertriglyceridemic pancreatitis (HTGP) accounts for up to 10% of acute pancreatitis presentations in non-pregnant individuals and is the third most common cause of acute pancreatitis after alcohol and gallstones. There are a number of retrospective studies and case reports that have suggested a role for apheresis and insulin infusion in the acute inpatient setting. We report a case of HTGP in a male with hyperlipoproteinemia type III who was treated successfully with insulin and apheresis on the initial inpatient presentation followed by bi-monthly outpatient maintenance apheresis sessions for the prevention of recurrent HTGP. We also reviewed the literature for the different inpatient and outpatient management modalities of HTGP. Given that there are no guidelines or randomized clinical trials that evaluate the outpatient management of HTGP, this case report may provide insight into a possible role for outpatient apheresis maintenance therapy.

**Key words:** Apheresis; Pancreatitis; Plasmapheresis; Outpatient; Hypertriglyceridemia

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**Core tip:** There are a number of retrospective studies that have suggested a role for apheresis and insulin infusion in the acute management of hypertriglyceridemic pancreatitis (HTGP) but the post-discharge course and outpatient management of HTGP remain unclear. We report a case of HTGP in a male with hyperlipoproteinemia type III who was treated successfully with insulin and apheresis on the initial inpatient presentation followed by bi-monthly outpatient maintenance apheresis sessions for the prevention of recurrent HTGP. We also reviewed the literature for the different inpatient and outpatient management modalities of HTGP.

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## INTRODUCTION

Hypertriglyceridemic pancreatitis (HTGP) accounts for up to 10% of acute pancreatitis presentations in non-pregnant individuals and is the third most common cause of acute pancreatitis after alcohol and gallstones<sup>[1,2]</sup>. Both genetic and secondary causes of lipoprotein metabolism have been implicated in HTGP. A serum triglyceride (TG) level of 10 g/L or greater is associated with acute pancreatitis. The risk of HTGP is approximately 5% with TG levels above 10 g/L and 10% to 20% with TG > 20 g/L<sup>[3]</sup>. The 2013 American College of Gastroenterology (ACG) guidelines in managing acute pancreatitis recommend obtaining a triglyceride level on all patients with acute pancreatitis without a known history of alcoholism or gallstones. While the ACG guidelines extensively explore the management of pancreatitis in general, there is a lack of data on the specific management of HTGP<sup>[4]</sup>. A number of retrospective studies and case reports in the past decade have suggested a role for insulin infusion with or without apheresis as an approach to rapidly lowering TG levels in an attempt to treat HTGP<sup>[1,5-18]</sup>. There are no randomized clinical trials evaluating the benefit of insulin infusion or apheresis in managing HTGP. Furthermore, there is a lack of characterization of post-discharge course and outpatient management of HTGP<sup>[19,20]</sup>. To our knowledge, there is only one case report of two patients with HTGP in 1996 who were managed with monthly plasmapheresis as maintenance therapy to prevent HTGP recurrence<sup>[21]</sup>. We report a case of HTGP in a male with hyperlipoproteinemia type III who was treated successfully with insulin and apheresis followed

by bi-monthly maintenance apheresis sessions post-discharge as prevention of recurrent HTGP. This case report may provide insight into a possible role for outpatient apheresis maintenance therapy.

## CASE REPORT

A 40-year-old Caucasian male with a past medical history significant for hyperlipoproteinemia type III (on atorvastatin 80 mg daily, fenofibrate 200 mg daily and omega-3 polyunsaturated fatty acids), coronary artery disease status post 3-vessel coronary artery bypass graft, peripheral vascular disease, hypertension, diabetes mellitus (DM) type 2, and one reported episode of acute pancreatitis in the past presented with epigastric pain, nausea and decreased oral intake over 3 d. Physical exam was remarkable for tachycardia to 100 beats/min, localized epigastric tenderness, and xanthomas with striae palmaris. Labs were remarkable for mildly elevated lipase of 334 U/L (reference range 114-286 U/L) and TG levels of 45.3 g/L (reference range 0-149). Abdominal CT scan showed moderate fat stranding around the pancreas and stable pseudocyst. He was started on insulin drip at a rate of 1 unit/h. TG levels trended down after 3 d of insulin infusion to 9.57 g/L. The patient, however, continued to have severe abdominal pain and inability to tolerate oral intake. After 3 d of inpatient stay, patient received his first session of apheresis. After 24 h of apheresis, patient improved symptomatically and was able to tolerate oral intake. Triglyceride levels trended down to 4.61 g/L after 24 h of apheresis and were 6.75 g/L on the day of discharge.

Given that the patient had a complicated cardiac history and that this was his second HTGP presentation in one year, a decision was made to have the patient undergo maintenance apheresis sessions bi-monthly as an outpatient to prevent recurrent pancreatitis and cardiac complications. Patient was discharged on home cardiac medications which consisted of hydrochlorothiazide 12.5 mg daily, Plavix 75 mg daily, aspirin 325 mg daily, metoprolol tartrate 50 mg BID, atorvastatin 80 mg daily, fenofibrate 200 mg and omega-3 polyunsaturated fatty acids. Twelve mo post-discharge course was remarkable for a total of three admissions due to recurrent pancreatitis with one admission attributed to poor adherence to apheresis, fat-free diet and lipid lowering medications. His TG levels mostly remained otherwise successfully below 15 g/L. Repeat abdominal CT scans over 12 mo demonstrated resolution of previous pseudocyst and absence of local complications (Figure 1).

## DISCUSSION

Patients with HTGP present with symptoms typical of

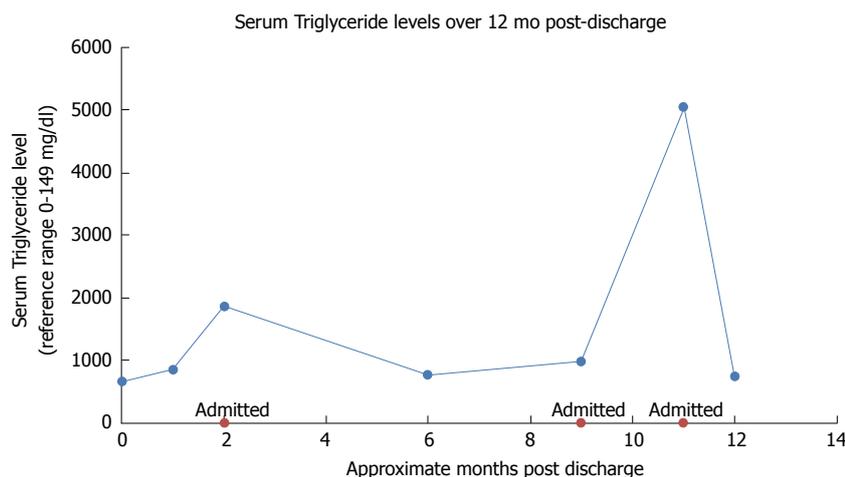


Figure 1 Serum triglyceride levels over 12 mo post-discharge. Hospital admissions are highlighted in red.

acute pancreatitis<sup>[1]</sup>. Specific features of HTGP that can help identify the etiology include xanthomas on extensor surfaces of arms and legs, lipemia retinalis and hepatosplenomegaly<sup>[22]</sup>. Lactescent serum is found in 45% of patients with mean Hypertriglyceridemia (HTG) level of 4537<sup>[2]</sup>. A serum TG level of 10 g/L or greater is associated with acute pancreatitis. The risk of HTGP is approximately 5% with TG levels above 10 g/L and 10% to 20% with TG > 20 g/L<sup>[23]</sup>. HTG by itself is not toxic to the pancreas, however, the breakdown of TG into free fatty acids (FFA) by pancreatic lipase causes lipotoxicity during acute pancreatitis, leading to a systemic inflammatory response<sup>[22]</sup>. Primary HTG that includes Frederick's phenotype I - V is associated with HTGP. Our patient was diagnosed with hyperlipoproteinemia type III, an autosomal recessive trait, characterized by presence of Apo E2/E2<sup>[24]</sup>. Apo E ligand clears chylomicrons and Very low-density lipoprotein (VLDL) remnants from the circulation. Thus, this disorder leads to accumulation of VLDL and chylomicrons leading to HTG. Secondary HTG is caused by DM, alcoholism, hypothyroidism, pregnancy, and certain medications such as thiazides, beta blockers, corticosteroids, isotretinoin, immunosuppressants and antipsychotics<sup>[1]</sup>.

A number of retrospective studies and case reports in the past decade suggested a role for insulin infusion with or without apheresis as an approach to rapidly lower TG levels in an attempt to treat HTGP<sup>[1,5-18]</sup>. There are no randomized clinical trials evaluating the benefit of insulin infusion, heparin or apheresis in managing HTGP to date. However, lowering of TG levels to below 5 g/L has been shown to advance clinical improvement in HTGP<sup>[25]</sup>. Apheresis is used to lower triglyceride level > 10 g/L and improve signs of severe inflammation such as hypocalcemia and lactic acidosis. One study reported (average TG of 14.06 g/L) a 41% decrease in TGs after one session of plasma exchange<sup>[18]</sup>. To our knowledge, there is only one case report of two

patients with severe HTGP in 1996 who were managed with monthly plasmapheresis maintenance therapy<sup>[21]</sup>. Their 32-38 mo course was remarkable for only one episode of acute pancreatitis in one patient, suggesting a beneficial role for maintenance plasmapheresis<sup>[21]</sup>.

With regard to anticoagulation during apheresis, studies have shown that citrate as opposed to heparin is associated with decreased mortality<sup>[18]</sup>. Intravenous insulin has been shown to be more effective than subcutaneous insulin in managing HTGP<sup>[26]</sup>. Insulin increases lipoprotein lipase which in turn accelerates chylomicron and VLDL metabolism to glycerol and FFA. It also inhibits lipase in adipocytes. Heparin is controversial in efficacy when used alone. It is thought to stimulate the release of endothelial lipoprotein lipase into the circulation, but the mechanism of lowering TG remains unclear<sup>[27]</sup>.

Lipid lowering agents are indicated in the management of HTGP<sup>[25]</sup>. However, this is further complicated by the association between statin therapy and the development of acute pancreatitis. A series of case-control studies in Taiwan demonstrated that individuals using a statin therapy for the first time are more likely to develop an episode acute pancreatitis when compared to individuals who are not on statin therapy. These studies included Simvastatin (OR = 1.3, 95%CI: 1.02-1.73), Atrovastatin (OR = 1.67, 95%CI: 1.18-2.38), and Rosuvastatin (OR = 3.21, 95%CI: 1.70-6.06)<sup>[28-31]</sup>. Table 1 provides a summary of HTGP management strategies.

In summary, we presented a case of HTGP in a male with hyperlipoproteinemia type III who was treated successfully with insulin and apheresis followed by outpatient bi-monthly maintenance apheresis sessions with a 12 mo post-discharge course remarkable for total of three admissions due to recurrent pancreatitis but with TG levels mostly remaining successfully below 15 g/L and repeat abdominal imaging demonstrating resolution of previous pseudocyst and absence of local

**Table 1 Summary of hypertriglyceridemic pancreatitis management strategies**

Management strategy	Description	Indication	Outcomes	Case report/Ref.
Diet restriction	Absolute restriction of fat intake	HTG, Primary prevention	Effective when combined with lipid lowering agents <sup>[15]</sup>	Tsuang <i>et al</i> <sup>[15]</sup> , 2009
Lipid lowering agents	Fibrates (gemfibrozil 600 mg twice daily), niacin, N-3 fatty acids, statins	First line in HTG Adjuvant therapy in HTGP	Triglyceride level lowered about 60% by fibrates, about 50% by niacin, about 45% by omega-3 fatty acids <sup>[15]</sup>	Tsuang <i>et al</i> <sup>[15]</sup> , 2009
Apheresis	Therapeutic Plasma Exchange which is removal of plasma and replacement with colloid solution (albumin, plasma). Citrate is used as an anticoagulant. Goal is TGH < 500	HTGP without contraindication to Apheresis such as inability to obtain central access or hemodynamic instability	Appears to be effective based on multiple case reports and case series. about 41% decrease in HTG levels. Apheresis within 48 h associated with better outcomes <sup>[16]</sup>	Furuya <i>et al</i> <sup>[16]</sup> , 2002
Insulin	Intravenous regular insulin drip (0.1 to 0.3 units/kg/h). Goal is TGH < 500. Used alone or in combination with apheresis and/or heparin	Apheresis unavailable unable to tolerate apheresis hyperglycemia > 500	Intravenous insulin is more effective than subcutaneous <sup>[17]</sup> Effective in lowering triglyceride levels	Berger <i>et al</i> <sup>[17]</sup> , 2001
Heparin	Combined with insulin. Subcutaneous heparin 500 units BID in 2 case reports	Controversial in HTGP	Controversial. Associated with increased mortality when compared to citrate (both combined with apheresis) <sup>[18]</sup> .	Gubensek <i>et al</i> <sup>[18]</sup> , 2014
Periodic apheresis	Described in 2 patients as monthly apheresis in 1996	Recurrence prevention especially in noncompliant patients	Reported success in one case report (2 patients in 1996) <sup>[21]</sup> .	Piolot <i>et al</i> <sup>[21]</sup> , 1996

HTGP: Hypertriglyceridemic pancreatitis; HTG: Hypertriglyceridemia; BID: Bis in die; TGH: Triacylglycerol hadrolase.

complications. This may suggest a beneficial role for outpatient apheresis as maintenance therapy in HTGP patients.

## COMMENTS

### Case characteristics

A 40-year-old Caucasian male with a past medical history significant for hyperlipoproteinemia type III (on atorvastatin 80 mg daily, fenofibrate 200 mg daily and omega-3 polyunsaturated fatty acids), coronary artery disease status post 3-vessel coronary artery bypass graft, peripheral vascular disease, hypertension, diabetes mellitus type 2, and one reported episode of acute pancreatitis in the past presented with epigastric pain, nausea and decreased oral intake over 3 d.

### Clinical diagnosis

Physical exam was remarkable for tachycardia to 100 beats/min, localized epigastric tenderness, and xanthomas with striae palmaris.

### Differential diagnosis

Acute pancreatitis, gastritis, peptic ulcer disease, gastroenteritis, gastroesophageal reflux disease.

### Laboratory diagnosis

Labs were remarkable for mildly elevated lipase of 334 U/L (reference range 114-286 U/L) and triglyceride levels of 45.3 g/L (reference range 0-149 g/L).

### Imaging diagnosis

Abdominal CT scan showed moderate fat stranding around the pancreas and stable pseudocyst.

### Treatment

Insulin, apheresis, atorvastatin 80 mg daily, fenofibrate 200 mg and omega-3 polyunsaturated fatty acids.

### Related reports

There are a number of case reports in the literature that have demonstrated a benefit from apheresis and insulin therapy in the inpatient management of hypertriglyceridemic pancreatitis (HTGP). There is only one case report that have suggested a role for outpatient apheresis as a maintenance therapy.

### Term explanation

HTGP is acute pancreatitis caused by high levels of serum triglycerides. Apheresis is the process of removal and separation of blood components and replacement with colloid solution (albumin, plasma).

### Experiences and lessons

Multiple studies have demonstrated a role for apheresis in the acute management of HTGP. This case report suggests a role for outpatient apheresis in preventing recurrent attacks of HTGP.

### Peer-review

This is a nice case report on a timely topic: hypertriglyceridemia-induced acute pancreatitis and role for outpatient apheresis maintenance therapy. This manuscript is generally of interest. The authors provided the complete review of this issue. The manuscript provides the updated evidence to the readers. It can be accepted for publication.

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