Therapeutic Plasma Exchange in Patients with Hypertriglyceridemic Pancreatitis: *When is it indicated?*

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Disclosure of Conflicts of Interest

"Therapeutic Plasma Exchange in Patients with Hypertriglyceridemic Pancreatitis"

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Introduction

- Hypertriglyceridemic pancreatitis (HP, HTGP) is characterized by severe hypertriglyceridemia (sHTG: triglyceride >1000-2000 mg/dl), acute pancreatitis (AP), and absence of other causes.
- HP is a potentially fatal complication of acute pancreatitis with an incidence of ~18 deaths/100,000 cases/year (0.00018).
- Complications of sHTG include: abdominal pain (nausea/vomiting), acute pancreatitis, hepatosplenomegaly, eruptive xanthomas, lipemia retinalis, memory loss, dementia, and peripheral neuropathy.
- We report on the use of plasma exchange (TPE) to effectively treat patients (pts) with HP refractory to conventional medical therapy (lipid-free diet plus pharmaceutical interventions).

Hypertriglyceridemic Pancreatitis

ASFA 2013 TA Guidelines

HYPERTRIGLYCERIDEMIC PANCREATITIS

Incidence: 18/100,000/yr	Procedure TPE	Recommendation Grade 2C	Category III
# of reported patients*:100–300			
RCT	CT	CS	CR
0	1 (29)	12 (132)	33 (33)

Gavva C et al. Transfus Apher Sci 2016; 54 (1): 99-102 *(case series, 13 pts)*
Ramirez-Bueno A et al. Eur J Intern Med 2014; 25 (2): 160-163 *(case series, 11 pts)*
Stephanutti C et al. Ther Apher Dial 2013; 17 (2): 130-137 *(excellent review of 6 case series)*
Ewald N, Hans-Ulrich K. Clin Res Cardiol Supp 2012; 7: 31-35 *(review of pharma treatment)*
Stephanutti C et al. Artif Orgas 2009; 33 (12): 1096-1102 *(case series, 17 pts)*
Tsuang W et al. Am J Gastroenterol 2009; 104: 984-991 *(review of 5 small case series)*

He W, Lu N. Hepatogastroenterology 2015; 62 (138): 429-434 *(recent review)*
Valdivielso P et al. Eur J Intern Med 2014; 25 (8): 689-94 *(recent review)*
Scherer J et al. J Clin Gastroenterol 2014; 48 (3): 195-203 *(recent review)*

Hypertriglyceridemic Pancreatitis (HP)

Dx:

- Hypertriglyceridemia (HTG):
  - results from elevation in lipoproteins used for triglyceride (TG) transport
  - 1° causes (<10%): gene mutations of lipoprotein lipase (LPL) & apo C-II.
  - 2° causes: DM, excessive alcohol intake, high-carbohydrate diets, pregnancy, hypothyroidism, chronic renal disease, nephrotic syndrome, gallstone disease, and medications (corticosteroids, diuretics, estrogens, antiretrovirals, & retinoids).
  - complications occur: TG levels > 500-1000 mg/dl:
    - abdominal pain (N/V), acute pancreatitis, HSM, eruptive xanthomas, lipemia retinalis, memory loss, dementia, peripheral neuropathy, & dypsnea.
  - cause of AP: endothelial damage 2° free fatty acids & lysolecithin, lack of LPL activity, high plasma TG → activation of inflammatory mediators.
  - Severe hypertriglyceridemia (sHTG): rare cause of AP (1-4%)

- Hypertriglyceridemic Pancreatitis (HP): characterized by sHTG (TG >1000-2000 mg/dl), acute pancreatitis, and absence of other causes.

Hypertriglyceridemic Pancreatitis (HP)

Standard Treatment Options (of HP):

- lipid lowering agents (fibrates, nicotinic acid, statins [↓ LDL-cholesterol])
- bowel rest (no oral intake, moderate caloric restriction, occas. TPN w/o lipids)
- IV hydration (↓ hyperviscosity)
- insulin (in setting of hyperglycemia; activates LPL)
- heparin (releases LPL from endothelial stores enhancing TG clearance)
  - may exacerbate bleeding into pancreatic bed (use is controversial)

Hypertriglyceridemic Pancreatitis (HP)

Adjunctive Treatment (of HP):

- plasma exchange (TPE):
  - CR, CS, & single CT (nonrandomized, w/historic controls): use of TPE in HP
  - ↓ TG levels: 46-85% with ↓ symptoms of AP (after 1-3 TPE txs)
  - CT (Chen et al, 2004): no difference in pts with HP (standard therapy [ST] & TPE (n=10) versus ST alone [n=19]: re mortality, systemic & local complications.
    - limitations: 1) groups may not be comparable; 2) negative findings may be 2° to delayed initiation of TPE (authors recommend earlier intervention); 3) time from diagnosis to start of TPE not provided.
  - TPE in pregnant women w/HP (8 CRs; fibrate assoc. w/teratogenic effects):
    - TPE (median 2 txs, range 1-10), w/cesarian due to fetal distress (5/6 CRs)
    - Prophylactic TPE 2° h/o AP (2 CRs): CR #1: 6 TPEs (Q7-10d), starting 25 wks gestation; CR #2: 13 TPEs, starting 19 wks gestation. Healthy infants delivered 34 wks. Goal: maintain TG levels < 1000 mg/dl.
  - Recurring pancreatitis (2 CS, 8 pts): TPE ↓ frequency of AP episodes (larger series of 6 pts, frequency ↓ 67%); goal: maintain TG levels < 150 mg/dl.

Severe Hypertriglyceridemia-Related Acute Pancreatitis

Claudia Stefanutti,[1,2] Giancarlo Labbadia,[3] and Claudia Morozzi[1,2]

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Excellent review article (2013): of 5 recent cases series (see below):

- Prognosis after TPE may depend upon early initiation of tx (rec TPE w/i 24 hrs)
- TPE superior to DFPP (to ↓ excess TG; tendency of TG to clog pores of filters)
- Other recommendations:

1) 5000 units IV heparin (pre-tx) → use ACD-A during TPE tx
2) Replacement fluid: 5% albumin, 1.5 PV
3) Goal: TG < 500 mg/dl

TABLE 1. *Current available studies on the use of apheresis in the treatment of severe hypertriglyceridemia (sHTG) (only studies with patients* n ≥ *10)*

Reference	Patients included	Plasma exchange methods	Significant reduction of tryglicerides
Stefanutti et al. (34)	17	Albumin	By 61%
Yeh et al. (22)	18	FFP and albumin, double membrane filtration	By 66% (first setting) and by 83% (second setting)
Yeh et al. (21)	17	FFP and albumin	Significant reduction
Chen et al. (20)	94	FFP and albumin	n.a.
Gubensek et al. (22)	50	Albumin	Significant reduction
Kyriakidis et al. (6)	10	FFP	By 62%

FFP, fresh-frozen plasma; n.a., not available. Reproduced from Ewald and Kloer (20) with kind permission from Springer Science+ Business Media.

Stephanutti C et al. Ther Apher Dial 2013; 17 (2): 130-137

Severe Hypertriglyceridemic-Related Acute Pancreatitis

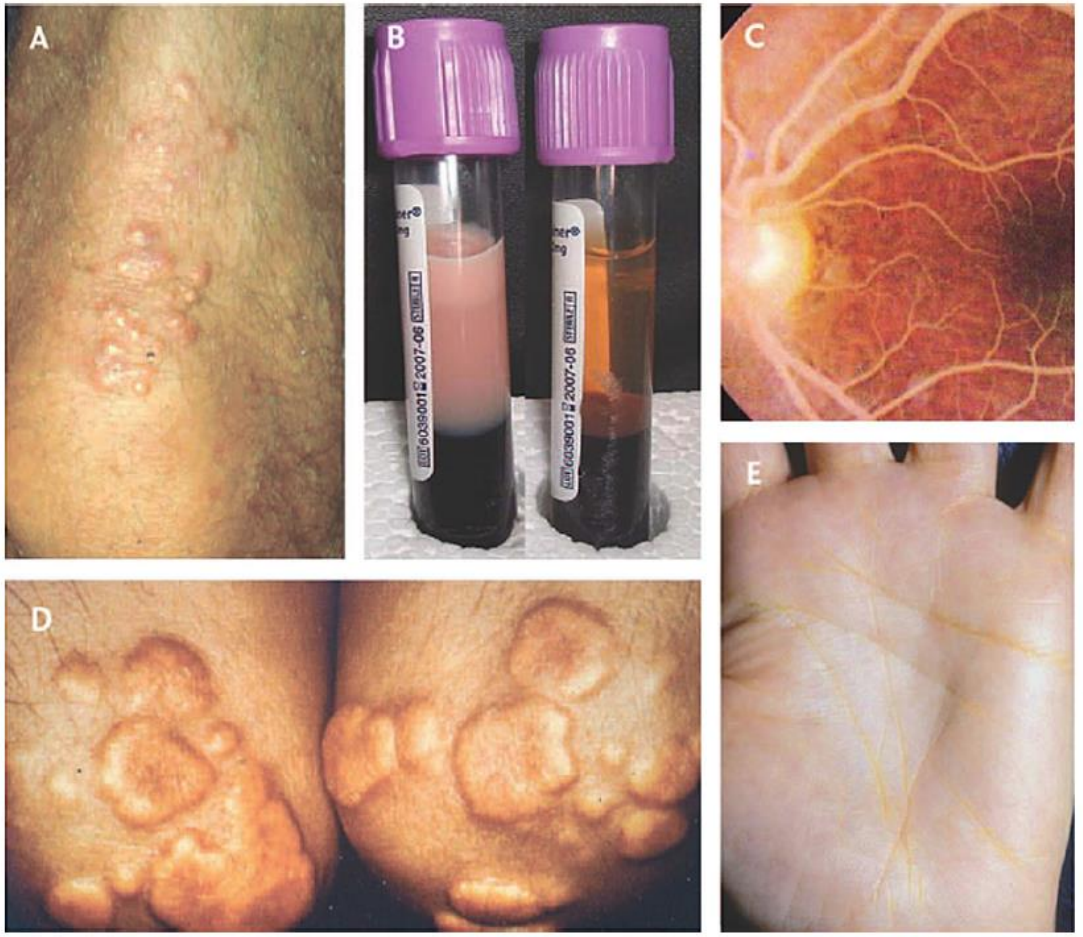

FIG. 1. Primary hypertrygliceridemia (reproduced from Yuan et al. (12)). Used with permission from the *Canadian Medical Association Journal*.

Stephanutti C et al. Ther Apher Dial 2013; 17 (2): 130-137

Treatment options for severe hypertriglyceridemia (SHTG): the role of apheresis

Nils Ewald · Hans-Ulrich Kloer

Table 1 Pharmacological treatment options for SHGT

Treatment modality	Mechanism of action	Comments	Limitations
Fibrates	Increase of LPL level, decrease in hepatic TG synthesis by induction of hepatic FFA oxidation, and stimulation of reverse cholesterol transport	Considered drugs of first choice	Slow onset of TG lowering
Nicotinic acid	Reducing VLDL secretion via receptor	Reliable long-term effect on TG level	Prominent side effects such as facial flushing, slow onset of TG lowering
HMG-CoA reductase inhibitors	Inhibition of cholesterol synthesis	Only of use in combination with other drugs such as fibrates in order to achieve synergistic effects	Higher risk of myositis or myopathy, no drug of first choice
Omega-3-FA	Reduced hepatic TG synthesis, enhanced peroxisomal β-oxidation, increased LPL activity and adipose tissue LPL expression	Potent drug with no side effects, immediate onset of action	No limitations
MCT	No chylomicron formation, no chylomyicron synthesis, induction of michondrial β-oxidation of FA	Immediate onset of action on TG levels	No limitations
Insulin	Activation of LPL (acceleration of chylomicron degradation)	Useful especially in the treatment of poorly controlled diabetic subjects with HTG	Only of limited efficiency
Heparin	Stimulation of release of endothelial LPL	Not recommended as a monotherapy	Cave: increased LPL degradation and depletion of LPL plasma stores

Note carefully that conventional treatment of any comorbidity, e.g., pancreatitis is imperative as well as screening for secondary causes of HTG and treatment of the underlying disease

LPL lipoprotein lipase; *TG* triglycerides; *FA* fatty acids; *FFA* free fatty acid; *VLDL* very low density lipoproteins; *HMG-CoA* hydroxymethylglutaryl-coenzyme-A; *MCT* medium-chain triglycerides; *HTG* hypertriglyceridemia

Ewald N, Hans-Ulrich K. Clin Res Cardiol Supp 2012; 7: 31-35.

Treatment Options For Severe Hypertriglyceridemia: the role of apheresis

Table 3 Suggested treatment regime for SHGT

Acute treatment in severe HTG (TG > 1000 mg/dl)	Long-term treatment for the prevention of severe HTG episodes (TG levels to be reached 300–500 mg/dl)
Apheresis until plasma TG level < 1000 mg/dl	Dietary measurements
MCT and omega-3-FA in combination	<20 g LC-FA/day, abstinence of alcohol
	Adding omega-3-FA (> 3 g EPA+DHA)
	Adding fibrates to omega-3-FA
	Adding nicotinic acid to fibrates, omega-3-FA
	Considering recurrent episodes of plasmapheresis

Note carefully that conventional treatment of any comorbidity, e.g., pancreatitis is imperative as well as screening for secondary causes of HTG and treatment of the underlying disease

HTG hypertriglyceridemia; *TG* triglycerdies; *FA* fatty acids; *MCT* medium-chain triglycerides; *LC-FA* long-chain fatty acids; *EPA* eicosapentaenoic acid; *DHA* docosahexaenoic acid

Ewald N, Hans-Ulrich K. Clin Res Cardiol Supp 2012; 7: 31-35

Hypertriglyceridemic Pancreatitis: Presentation and Management

Wayne Tsuang, MD[1], Udayakumar Navaneethan, MD[1], Luis Ruiz, MD[2], Joseph B. Palascak, MD[3] and Andres Gelrud, MD, MMSc[4]

Review of 5 case series:

Table 1. Apheresis in hypertriglyceridemic pancreatitis (reports with five or more patients)

Study	No. of patients	No. of patients with complete recovery (%)	Mortality (%)
Chen *et al.* (56)	20	0 (100)	0
Yeh *et al.* (64)	17	13 (76.5)	2 (11.8)
Kyriakidis *et al.* (61)	10	9 (90)	1 (10)
Kadikoylu *et al.* (59)	7	7 (100)	0
Lennertz *et al.* (62)	5	5 (100)	0

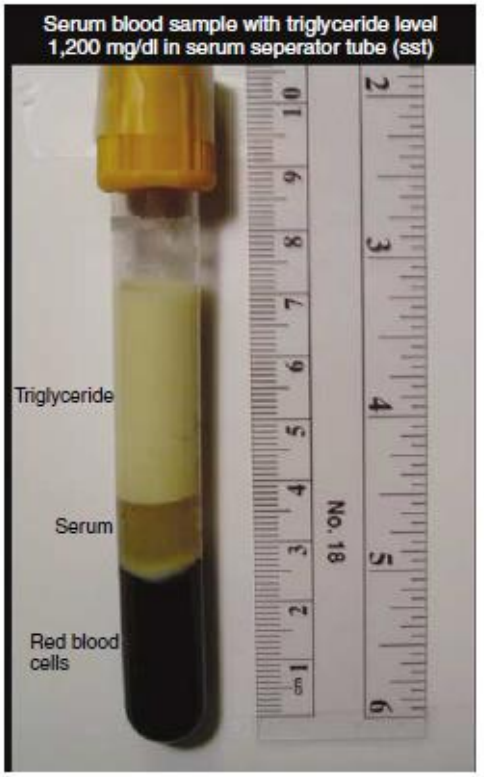

Figure 1. Lactescent sample.

Tsuang W et al. Am J Gastroenterol 2009; 104: 984-991

Tsuang W et al. Am J Gastroenterol 2009; 104: 984-991

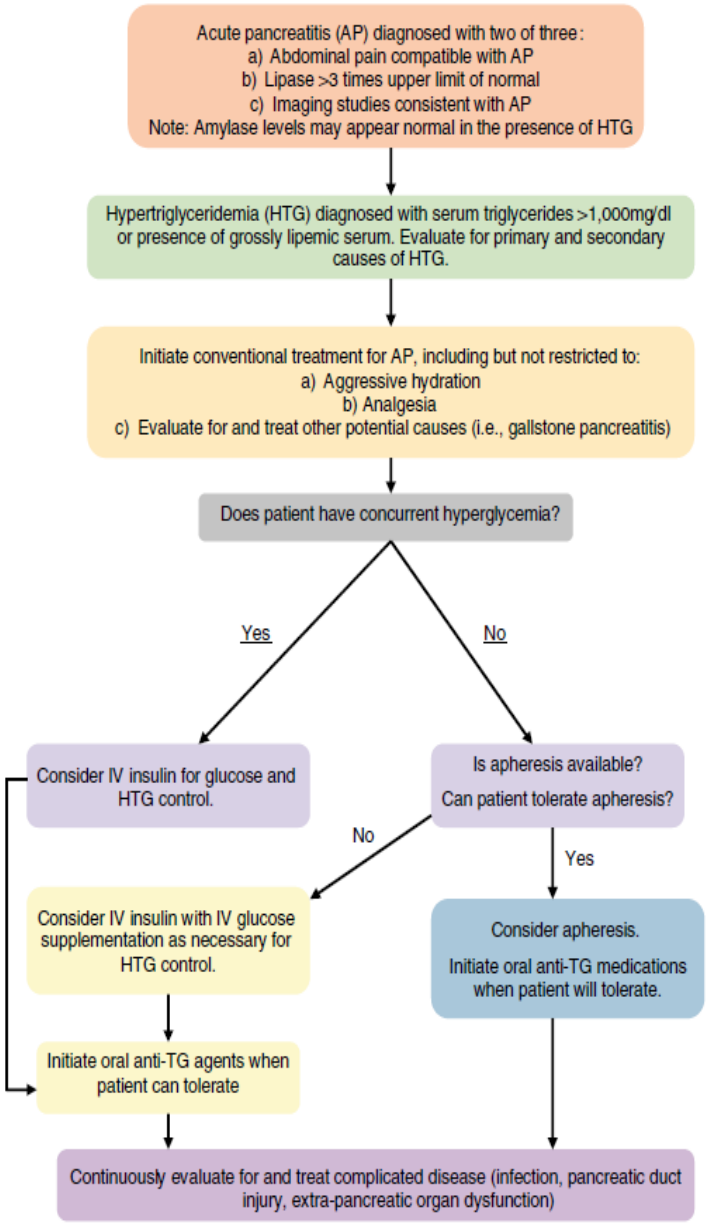

Figure 2. Proposed approach to hypertriglyceridemic pancreatitis.

Hypertriglyceridemic Pancreatitis (HP)
(retrospective cohort study, 1/09-4/16)

Retrospective Review: 37 pts dx'd with HP (1/09-4/16, ~7.4 yrs): ~4.9 pts/yr:
(retrospective cohort study)

Characteristic (Baseline)	TPE & ST	ST alone
# patients	24/37 (65%)	13/37 (35%)
Age (mean): 37 y.o. (16-79)	35 y.o. (16-58)	41 y.o. (27-79)
Female gender: 58%	62% female	51% female
Ethnicity (% Caucasian): 61%	57% caucasian	66% caucasian
Mean TG level (<150 mg/dl)	6,376# (4652-12486)	2,998# (1697-4120)
Mean lipase (73-393 U/L)	1,719 (797-2745)	956 (472-1796)
Mean amylase (25-115 U/L)	data incomplete	data incomplete
# TPE (median/mean)	2/2.55 (1-4)	0

ST: standard treatment; TG: triglycerides; #: mg/dl

Hypertriglyceridemic Pancreatitis (HP)

(retrospective cohort study, 1/09-4/16)

Treatment	**TPE & ST**	**ST alone**
# patients	24/37 (65%)	13/33 (35%)
Mean TG level (<150 mg/dl)	6,376# (4652-12486)	2,998# (1697-4120)
# TPE (median/mean)	2/2.55 (1-4)	0
Heparin	19/24 (79%)	8/13 (62%)
Insulin	22/24 (92%)	11/13 (85%)
Dietary restriction (NPO)	100%	100%
Lipid lowering agents (2-3 agents)	100%	100%
Replacement fluid	5% albumin (16/24: 75%) albumin/FFP (5/24: 21%) FFP (1/24: 4%)	NA
Anticoagulant (for TPE)	ACD-A (100%)	NA
Mean TG level (after 2 TPE/48 hrs)	1,589# (627-3815)	1,321# (487-2468)

ST: standard treatment; TG: triglycerides; #: mg/dl

Hypertriglyceridemic Pancreatitis (HP)
(retrospective cohort study, 1/09-4/16)

Final Results	**TPE & ST**	**ST alone**
# patients	24/37 (65%)	13/33 (35%)
Mean TG level (<150 mg/dl)	6,376# (4652-12486)	2,998# (1697-4120)
# TPE (median/mean)	2/2.55 (1-4)	0
Mean TG level (after 2 TPE/48 hrs)	1,589# (627-3815)	1,321# (487-2486)
Decrease in mean TG level (p>0.05)	↓75% (6376→1589)	↓56% (2998→1321)

- Despite a larger decrease in TG levels seen in the TPE & ST group (vs the ST group, 75% vs 56%), both groups experienced marked improvement in clinical symptoms of pancreatitis and hyperglycemia.

ST: standard treatment; TG: triglycerides; #: mg/dl

Hypertriglyceridemic Pancreatitis (HP)
(retrospective cohort study, 1/09-4/16)

Retrospective Review: 37 pts dx'd with HP (1/09-4/16, ~7.4 yrs): ~4.9 pts/yr:

Limitations (of retrospective cohort study):

1) lack of long-term follow-up:
   a) no mortality data
   a) does adjunctive PE decrease the frequency of recurrent pancreatitis episodes?
2) no comparative data on length of stay
3) 1.2-1.5 PV (vs. 1 PV) would have yielded larger % decrease in TG
4) lack of complete data on ST patients

Hypertriglyceridemic Pancreatitis (HP): Summary

Utility of TPE as Adjunctive Treatment (of HP):

- plasma exchange (TPE):
  - TPE rapidly ↓ TG levels (effect is transient); need adequate lipid lowering tx
  - TPE superior to DFPP (to remove excess TG)
  - Replacement fluid: most studies used 5% albumin (some used FFP as it contains LPL and could enhance TG removal).
  - Frequency: daily TPE (X 1-3 txs depending on pt response and TG levels)
  - Starting TPE: starting early vs waiting to see if improvement w/standard tx
  - TPE in pregnant women w/HP: useful, less controversial (↓ fibrate use)
  - No RCTs (given current data, makes sense to consider multi-center RCT)

Summary

- Plasma exchange (in conjunction with other supportive therapies) is very effective in rapidly lowering triglyceride levels in patients with hypertriglyceridemic pancreatitis.
- However, aggressive supportive therapies may be nearly as effective (as plasma exchange) in rapidly lowering triglyceride levels (and helping to control clinical sequellae of hypertriglyceridemia) when plasma triglycerides are < 2500-3500 mg/dl.
- The design of thoughtful randomized trials to test this theory and validate (or refute) the concept of a threshold triglyceride level (or range) would help in the optimal use of TPE in hypertriglyceridemic pancreatitis.

Thank you for your attention

Questions?