

# World Journal of *Clinical Cases*

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## Therapeutic plasma exchange for hyperlipidemic pancreatitis: Current evidence and unmet needs

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### Abstract

With changes in lifestyle and diet worldwide, the prevalence of hyperlipidemic acute pancreatitis (HLAP) has greatly increased, and it has become the most common cause of acute pancreatitis not due to gallstones or alcohol. There are many available therapies for HLAP, including oral lipid-lowering agents, intravenous insulin, heparin, and therapeutic plasmapheresis (TPE). It is believed that the risk and severity of HLAP increase with rising levels of serum triglycerides (TG), thus a rapid decrease in serum TG level is the key to the successful management of HLAP. TPE has emerged as an effective modality in rapidly reducing serum TG levels. However, due to its cost and accessibility, TPE remains poorly evaluated until now. Some studies revealed its efficacy in helping to treat and prevent the recurrence, while some studies suggested that TG levels were not correlated with disease severity, mortality, or length of hospital stay. Thus TPE might have no beneficial effect for the outcome. This article gives an overview of the published evidence of TPE in the treatment of HLAP and outlines current evidence regarding individual outcome predictors, adverse effects of the procedure, and TPE in special occasions such as for pregnant patients and patients with diabetic ketoacidosis. Future direction of TPE research for HLAP is also discussed in this review.

**Key Words:** Therapeutic plasma exchange; Hyperlipidemic acute pancreatitis; Evidence; Outcome; Future direction

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**Core Tip:** Prevalence of hyperlipidemic acute pancreatitis has greatly increased and has become the most common cause of acute pancreatitis not due to gallstones or alcohol. Although therapeutic plasmapheresis has emerged as an effective modality in rapidly reducing serum triglyceride levels and has been used for hyperlipidemic acute pancreatitis clinically, the exact role of therapeutic plasmapheresis in the disease course is unclear and remains poorly evaluated. We herein outline the current evidence and discuss the future research directions.

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## INTRODUCTION

The association between hyperlipidemia and acute pancreatitis (AP) was first described by Speck in 1865[1]. AP is an acute, painful abdominal disease involving the pancreas with the incidence ranging from 13 to 56 per 100000 persons per year[2-4]. Gallstones and alcohol abuse are the two most common causes of AP, while hypertriglyceridemia (HTG) has become the third most common cause of AP with a reported incidence of 2%-4% [5,6]. Hyperlipidemic acute pancreatitis (HLAP) is defined as triglyceride (TG) levels greater than 11.3 mmol/L or TG levels greater than 5.65 mmol/L with grossly lipemic serum[7]. The typical clinical profile of HLAP is a patient with pre-existing lipid abnormality along with the presence of secondary factors that can induce HTG. Clinically, poorly controlled diabetes mellitus, alcohol abuse, pregnancy, or a medication are the most common causes[1]. Compared with biliary pancreatitis and alcoholic pancreatitis, the clinical severity and the rate of complications with HLAP are generally higher[8,9].

There are many available therapies for HLAP, including oral lipid-lowering agents, intravenous insulin, heparin, and therapeutic plasmapheresis (TPE)[10]. HLAP occurs in the presence of severe HTG (TG > 5.6–11.3 mmol/L). Therefore, a rapid decrease of serum level and the maintenance of serum TG at levels < 5.65 mmol/L are the keys to the successful management of HLAP[11]. Conservative treatment, including fasting, lipid-lowering drugs, insulin, or fluid restoration might decrease TG levels in a time span of days to weeks, whereas TPE might decrease TG levels rapidly in hours[12]. Over the years, numerous case reports or small series have been reported on the use of TPE in HLAP patients. However, most reports are mainly retrospective, while well-designed prospective comparative studies are lacking. Due to variability in patient selection and the uncertainty on ameliorating the outcome, the role of removing excess TG from the serum in these patients remains unclear.

In this review, we collect the current evidence regarding TPE in the treatment of HLAP, analyze the role of TPE in reducing TG levels, highlight the impact of TPE on the outcome of the disease, and analyze TPE on special occasions such as for pregnant patients and patients with diabetic ketoacidosis (DKA). We aim to analyze which HLAP patients can benefit from TPE and to propose the future direction for TPE study from the clinical view.

## INCIDENCE/PREVALENCE OF HLAP

Since first described in 1865[1], HLAP has shown a rising incidence worldwide as a result of increasing obesity-related dyslipidemia[13]. The cause for high serum TG can be either genetic or acquired in origin. Acquired causes include uncontrolled diabetes mellitus, alcohol abuse, pregnancy, medications, hypothyroidism, nephrotic syndrome, and high carbohydrate diets[14]. According to the definition, most experts agree that AP related to TG levels above 5.6 mmol/L should be considered as suspected HLAP, and AP associated with TG levels over 11.3 mmol/L is confirmed as HLAP[15]. There is a 5% possibility of developing AP if TG levels exceed 11.3 mmol/L, and it rises to 10%–20% if TG levels elevate over 22.6 mmol/L[10].

The incidence of AP in the United Kingdom is about 56 cases per 100000 persons per year[2]. Gallstone, alcohol, and hyperlipidemia are the three most common causes of AP globally, whereas in China, hyperlipidemia has exceeded alcohol to become the second major cause of AP[5]. In alignment to these findings, another report from a 716 case cohort study by Mosztbacher *et al*[16] demonstrated that 30.6% of the patients presented with elevated TG levels ( $\geq 1.7$  mmol/L) in which 7.7% of AP cases had TG levels above 11.3 mmol/L, which is considered as a causative etiological factor.

HLAP appears to be more prevalent in males than females in younger patients (age < 50 years)[17]. During pregnancy, HLAP is largely related to familial HTG with the incidence estimated to be 1 in 25000 pregnancies[18]. In one of the studies, HLAP was reported in 30% of pregnant patients with AP[19].

## RELATIONSHIP BETWEEN SERUM TG LEVELS AND DISEASE SEVERITY

HTG is defined as serum TG level greater than 1.70 mmol/L, with very severe cases greater than 11.3 mmol/L. The incidence of AP in patients with TG > 11.3 mmol/L is 5%, which increases to 10%-20% with TG level > 22.6 mmol/L[10]. Although it has been proposed that HTG could worsen the course of AP in some reports, clinical studies evaluating the relationship between elevated TG levels and the severity of AP have had conflicting results[20]. A report by Kiss *et al*[21], which included 16 eligible studies with 11965 patients retrieved from PubMed and EMBASE, showed a significantly higher occurrence of pancreatic necrosis, persistent organ failure, and renal failure in groups with HTG. The rates of complications and mortality for AP were significantly increased in patients with TG > 5.6 mmol/L or > 11.3 mmol/L *vs* < 5.6 mmol/L or < 11.3 mmol/L, respectively, while no significant difference in AP severity based on the extent of HTG.

A study by Mosztbacher *et al*[16], which enrolled 716 cases, showed that TG levels above 11.3 mmol/L were associated with a significantly higher rate of moderately severe AP (group with TG < 1.7 mmol: Moderately severe AP 22.6% *vs* group with TG 11.3-22.59 moderately severe AP 66.7%). The rate of severe AP in the group with TG  $\geq 22.6$  was higher than that in the group with TG 11.3-22.59, whereas TG levels above 22.6 mmol/L was significantly related to severe AP as well. In a prospective international, multicenter AP registry study[16], data on 716 AP cases were analyzed. The data showed that the rates of local complications and organ failure and maximum C-reactive protein level were significantly and dose-dependently raised by HTG. TG above 11.3 mmol/L was linked to a significantly higher incidence of moderately severe AP and longer hospital stay, whereas TG over 22.6 mmol/L was significantly associated with severe AP as well.

Inconsistent with the reports as noted above, Gubensek *et al*[22] analyzed 103 patients of HLAP treated with TPE: The study revealed that TG levels at admission were not correlated to APACHE II or to the length of hospital stay. HTG may be either primary (types I, IV, and V) or secondary[23]. Owing to the small samples, many published reports or case series regarding association between TG levels and severity of the disease were not analyzed based on the etiology of HTG. Nevertheless, it is widely believed that TG concentrations are associated with a more complicated hospital course, including a need for admission to intensive care units, persistent multiorgan failure, and systemic inflammatory response syndrome indicating that it is desirable to lower the TG concentrations acutely in HLAP[24].

## TREATMENT MODALITIES FOR HLAP

Treatment of HLAP includes both the conventional treatment including pancreatic rest, supportive adequate fluid supply, pain control, and broad spectrum antibiotics if necessary[10] and requires a multimodal approach to lower TG levels. Current guidelines have not yet defined first-line TG-lowering therapies. Previous studies investigating the treatment of HLAP with insulin alone, insulin in combination with heparin, and/or TPE have been published[25,26]. TPE as a treatment for HLAP was first described in 1978[27] and has since then been a therapeutic modality in clinical practice.

## ROLE OF TPE FOR HLAP

In 1978, Betteridge *et al*[27] first described the use of apheresis for lowering TG levels, and apheresis has since then been a therapeutic modality for HLAP patients. Apheresis broadly describes the removal of blood components. A variety of techniques including plasmapheresis, plasma exchange, and low-density lipoprotein apheresis has been used with a goal of reducing disease severity. TPE is a procedure that removes plasma from the blood and replaces it with colloid or crystalloid solutions. It is believed that TPE removes available TG in very-low-density lipoprotein and chylomicrons from serum and prevents generation of free fatty acids, which causes local and systemic effects[28]. Also, TPE eliminates excess proteases, supplements protease inhibitors, and reduces the levels of pancreatic enzymes[12] and inflammatory cytokines, including interleukin-1 and tumor necrosis factor- $\alpha$ [29].

Plasma exchange is usually considered the first-line strategy to treat severe HTG if available[30]. Like many other hospitals in China, in our institute, TPE has become available around the clock and has been conducted routinely in treatment for HLAP. Although several observation studies have examined the efficacy of TPE, direct comparison of patients treated with or without TPE was not performed. HLAP is currently considered as category 3 indications in the American Society for Apheresis 2019 guideline; that is, it is a recommendation with low-quality or very-low-quality evidence, implying that the optimum role of apheresis is not established and decision making on apheresis use should be individualized[31]. Recent studies and evidence are mainly focusing on its efficacy in reducing elevated serum TG levels and whether this effect could lead to a better outcome.

### **TPE in reducing elevated serum TG levels**

The beneficial effect of TPE is believed to be due to a rapid decrease in TG levels, thus to halt the progression of HLAP. To date, numerous reports and several studies revealing the effectiveness of TPE in reducing TG levels have been published. A study by Yu *et al*[12] demonstrated that TPE decreases TG remarkably. In their report, a total of 132 patients with HLAP were analyzed. In 43 patients who underwent TPE, the 24 h TG clearance rate was 71% (62%-84%). A retrospective review reported by Fei *et al*[32] revealed that TPE reduced TG levels with an average reduction rate of 60.3%. Accordingly, Gubensek *et al*[22] reported that TPE reduced serum TG faster and more effectively than it could be expected with conservative treatment. In their study, 103 HLAP patients were treated with TPE (111 episodes); the mean reduction of TG level was 59%. Similarly, Yıldırım Şimşir *et al*[33] reported a TG reduction rate of 69.7% in a group of 31 cases treated with TPE. Moreover, according to the report by Kandemir *et al*[34], which included 33 HLAP patients who underwent TPE, the TG level decreased by 54.4% after one session and by 79.4% after a second session.

Although TPE results in a rapid lowering of TG, it is difficult to conclude that TPE has a higher TG lowering effect than treatment without TPE. Miyamoto *et al*[35] conducted a post hoc analysis of data obtained in the setting of a multicenter retrospective study of severe AP from 44 institutions. Of the 1159 patients enrolled, 30 had HLAP. The median serum TG was 2843 mg/dL. Ten patients were treated with TPE, while twenty were treated without TPE. The linear mixed-effect model did not find any significant association between the time-course of reduction in serum TG concentration and TPE. They compared 5 patients who underwent plasma exchange on the first day of admission with 10 patients who did not. No significant difference in median serum TG was found between these two groups. The authors concluded that TPE had no additional TG lowering effect in HLAP. Recent case series studies revealing the effect of TPE on TG clearance are summarized in Table 1.

### **TPE in ameliorating the outcomes**

The impact of TPE on disease severity has been demonstrated in a few case reports. Dehal and Adashek[36] reported a case of HLAP with severe systemic inflammatory response with TG levels of 1181 mg/dL; the patient developed acute respiratory distress syndrome and uremic encephalopathy. Two sessions of TPE were conducted with a rapid fall in serum TG levels, in turn leading to early clinical recovery. Gudivada *et al*[37] reported a case of HLAP. Over the course of the illness, the patient developed multiple organ failure. The patient received early conservative treatment including insulin infusion initially. TPE was conducted once hemodynamic stability was achieved. This approach improved the functioning of the organs. Moreover, Eden *et al*[38] reported a 36-year-old Caucasian woman with HLAP, who required invasive mechanical ventilation. The patient underwent TPE after which the TG levels and C-

**Table 1 Reports comparing triglyceride clearance rate and mortality between therapeutic plasma exchange and nontherapeutic plasma exchange groups**

Ref.	Year	Study design	Study size	TPE vs Non-TPE	24 h TG clearance rate	Mortality
Yu <i>et al</i> [12]	2020	Retrospective study	132	43 with TPE; 46 with IIT; 43 with NIIT	TPE: 71.00%; IIT: 68.00%; NIIT: 62.00%	TPE: 6.89%; IIT: 6.52%; NIIT: 2.00%
Fei <i>et al</i> [32]	2020	Retrospective study	8	All with TPE	60.30%	/
Gubensek <i>et al</i> [22]	2014	Retrospective cohort study	103	74 with early TPE; 29 with late TPE (conservative treatment followed by TPE)	Early TPE: 59%; Conservative treatment: 27%	Early TPE: 7%; Late TPE: 6%
Yildirim Şimşir <i>et al</i> [33]	2019	Retrospective study	31	All with TPE	69.70%	0
Kandemir <i>et al</i> [47]	2018	Retrospective study	33	All with TPE	54.40%	3.00%
Miyamoto <i>et al</i> [35]	2017	Retrospective study	30	10 with TPE; 20 without TPE	No difference between groups	TPE: 0%; Non-TPE: 10%
Biberici Keskin <i>et al</i> [39]	2019	Retrospective study	41	12 with TPE; 29 without TPE	TPE: 44%; Non-TPE: /	TPE: 25%; Non-TPE: 0

TG: Triglycerides; TPE: Therapeutic plasma exchange; IIT: Insulin intensive therapy; NIIT: Non-insulin intensive therapy.

reactive protein decreased dramatically, and her condition improved.

There is limited data from well-designed comparative studies regarding the impact of TPE on disease course. Biberici Keskin *et al*[39] retrospectively evaluated data of 41 patients with HLAP. Twelve of the patients underwent TPE. Patients undergoing TPE had more severe pancreatitis. Mortality was higher in patients who underwent TPE [3 (25.0%) *vs* 0,  $P < 0.01$ ]. There was no difference in terms of complications and recurrence rates between the two groups. Miyamoto *et al*[35] conducted a post hoc analysis on 1159 patients of which 30 had HLAP. Clinical outcomes including hospital mortality (0/10 *vs* 2/20) and pancreatic infection and requirement for invasive procedures (0/1 *vs* 2/20) did not differ significantly between two groups. Nakhoda *et al*[40] reported 10 HLAP patients admitted to the ICU. All patients had rapid reduction in TG levels after TPE, but only 5 had improvement in their APACHE II score. The APACHE II score did not differ statistically before and after TPE implementation. Additionally, Hutchison *et al*[41] retrospectively analyzed clinical and laboratory outcomes of HLAP patients treated without TPE. In 25 episodes among 24 patients, treatment included admission to ICU. There was no significant difference in mortality or rates of local complication, mechanical ventilation, or use of vasoactive medication or renal replacement therapy between this ICU subset and published cohorts. **Table 1** illustrates recent studies comparing clinical outcomes between groups treated with or without TPE.

Based on available data from clinical studies, definitive conclusions on the efficacy of TPE in reducing AP severity cannot be made. Considering the limitations that most clinical outcomes were analyzed based on small case samples, further randomized control studies would be needed to come to a definitive conclusion on the use of TPE for HLAP.

### **TPE for HLAP patients with DKA**

The coexistence of AP and DKA has been recognized since 1969[42]. Insulin deficit may lead to lipolysis and peripheral lipoprotein lipase inhibition, thus causing an increase in TG. Patients presenting with the triad of DKA, AP, and HTG can be challenging and might have higher risks if they present as not alert of past medical histories of diabetes mellitus upon admission[43].

TPE has been reported in the treatment for HLAP coexistent with DKA. Donelli *et al* [44] reported a 37-year-old man who was diagnosed with HLAP (TG 7000 mg/dL) coexistent with DKA. TPE was initiated with no insulin treatment after which the TG levels stabilized at 980 mg/dL. The patient developed uncompensated acidosis and elevated blood ketones. The patient was put on insulin, fluid replacement, and a nasogastric feeding tube. After 16 h, DKA completely resolved with normalization of pH, blood ketones, and the TG levels dropped to 260 mg/dL.

An HLAP patient concomitant with DKA may be exempt from TPE if DKA is managed properly. Yagnik *et al*[45] reported a 16-year-old AP patient concomitant with DKA and HTG. The patient had difficulty breathing and an altered mental status. Her serum TG level was 930 mg/dL with a “milky” appearance. The patient was put on continuous insulin drip along with conservative treatment. Her highest serum TG level was noted as 2515 mg/dL. Approximately 48 h after treatment, her condition improved with a downward trending of serum TG (614 mg/dL). The authors suggested that treatment for patients presenting with DKA and coexistent AP with severe HTG should focus first on appropriate DKA management. If treatment of DKA could resolve the severe HTG in an acceptable time frame, the need for TPE can be eliminated because with DKA resolution the HTG tends to nearly normalize.

### **TPE for HLAP in pregnant women**

During pregnancy, a progressive increase in serum TG levels is observed but rarely above 300 mg/dL[46]. The treatment of severe HTG in pregnant women is similar to other patients treated with TPE and/or intravenous insulin. There are no randomized controlled trials comparing efficacy of insulin and/or TPE for severe HTG, and thus treatment is usually based upon availability and preference.

Kandemir *et al*[47] reported a pregnant HLAP patient who was at the 28<sup>th</sup> week of gestation. TPE was performed thrice. After 3 sessions, her TG levels declined by 30.2%, 60.8%, and 75.9%. The patient was discharged on day six, and she gave birth to a healthy female infant at 38 wk of gestation.

TPE for HLAP patients during pregnancy can usually be eliminated if adequate conservative treatment was taken. Kilinc *et al*[48] retrospectively evaluated the records of 30 patients diagnosed with HLAP. In their report, 30 patients (20 females and 10 males) were included. Of 20 female patients, 12 patients were pregnant. All the patients were treated with insulin, low-molecular-weight heparin, and conservative treatments. Twenty-one patients were able to moderate the symptoms, while 9 patients did not respond and changed the modality to TPE treatment. Although 12 pregnant patients had higher TG levels initially, all 12 patients responded to standard therapy without TPE. Their TG levels and their pancreatitis were brought under control *via* insulin, low-molecular-weight heparin, and conservative treatments.

### **Predictors for TPE outcome**

Comprehensive models predicting treatment response to TPE are lacking. Several factors may exhibit a predictive value for TPE response, including clinical, radiography, serological features, and previous success or failure to TPE in a preceding relapse. Fei *et al*[32] analyzed 12 TPE procedures on 8 patients, the TG levels decreased by an average of 60.3%, and a 60.0% or greater reduction was achieved in 66.7% of all the procedures. However, they found that the degree of reduction for each procedure was not predictable, even among repeat procedures on the same patient.

Total cholesterol (TC) may serve as a possible predictor under specific conditions. Chen *et al*[49] conducted a retrospective case control study to determine the predicted function of TC on TG lowering effect in patients treated with TPE. Patients were categorized into high TC and low TC groups based on TC level of 12.4 mmol/L. TG reduction to below 500 mg/dL within 48 h served as the primary outcome. The study showed that more severe imaging manifestations and higher APACHE II score presented in the high TC group. In patients with elevated TC levels, the primary outcome occurred in 66.67% in those treated with TPE while 27.91% in those treated without TPE. In patients with lower TC levels, no significant difference was found in primary outcome between the TPE group and non-TPE group. The authors suggested that TC level could be a potential biomarker to predict the effects of TG lowering therapy in patients with HLAP.

### **Time to initiate TPE**

Time from symptom onset to TPE initiation has been of interest in clinical practice and remains unevaluated. A previous study revealed that delay in initiating TPE may be a potential reason for the lack of difference in mortality in patients treated with or without TPE[50]. A study from a cohort of 1233 patients with AP demonstrated that all major deleterious clinical outcomes including mortality were directly dependent on admission TG levels. Outcomes were improved by earlier presentation (< 24 h compared to 24–48 h from abdominal pain onset)[15]. A review by Garg and Rustagi [51] suggested TPE should be initiated preferably within 36 h provided the patient is able to tolerate the treatment. This time frame requires further investigation because another large retrospective study including 111 HLAP patients treated with TPE

showed no difference in mortality in the early (> 36 h) and late (within 36 h) TPE group[22].

Clinically, the timing for initiation of TPE needs to be individualized. Considering that insulin infusion can lower serum TG levels, either for diabetic or non-diabetic patients, some patients may be exempt from TPE. Based on available data reported and our experience, initiation within 24 h up to 96 h after the onset may be recommended as the best time frame because the effect of conservative treatment can be evaluated and the need for TPE be determined during this period.

### **Adverse effects/complications of TPE**

In terms of treatment safety, it is believed that TPE is a relatively safe procedure with few complications. Because TPE requires central intravenous access and transient anticoagulation, associated complications including allergy, infection, and deep venous thrombosis may develop. Kandemir *et al*[34] reported their observation. Thirty-three HLAP patients underwent TPE. Occurrence of vomiting in 5 patients, palpitation and tachycardia in 4 patients, and asymptomatic hypotension in 3 patients were observed. Two patients with hypervolemia, which was successfully treated with intravenous furosemide, and one patient with occlusion of the catheter were reported in their observation. Gubensek *et al*[22] reported a case with concomitant gastrointestinal bleeding from a Mallory-Weiss tear after TPE treatment with heparin anticoagulation. According to a report by Simsir *et al*[33], 3 (9.7%) out of 31 HLAP patients experienced complications related to TPE, including catheter infection in 2 patients and catheter thrombosis in 1 patient.

Another rare but life threatening complication is vascular complications. Yu *et al*[12] reported that the incidence of therapy-associated complications in the TPE group was significantly higher than that in the conservative group. Deep vein thrombosis was developed in one case, while no cases were found in the other groups. Accordingly, we reported a case of HLAP, although the patient's TG level reduced to normal range with symptoms relieved after TPE, the patient developed pulmonary embolism and multiple deep vein thromboses[52]. Although we cannot conclude that it was related to the TPE procedure, it arouses the awareness of this catastrophic complication.

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## **UNMET NEEDS AND FUTURE RESEARCH DIRECTIONS**

Despite the multitude of studies evaluating TPE for HLAP, three questions need consideration as future research directions. First: can TPE ameliorate the outcome? To date, only a few studies compared the outcomes of TPE *vs* conservative treatment. In addition, due to the small samples, comparison of mortality was inadequate. Most reports focus on the improvement of clinical symptoms and laboratory tests without the impacts of TPE on severity parameters (*e.g.*, organ failure, local complications). If mortality is used to assess the efficacy, a large sample is needed. Second: which patients with HLAP are most likely to benefit from TPE? As HLAP patients with poorly controlled diabetes or concomitant with DKA may respond to insulin treatment efficiently, on what conditions can patients be exempt from TPE, or in other words have no benefit from TPE? Third: to date, no patient-related response predictors for TPE outcome have been confirmed, thus parameters in screening candidates for TPE remain further exploration.

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## **CONCLUSION**

In this review we noted TPE to be highly efficacious in rapidly reducing serum TG levels. However, definitive conclusions on the efficacy of TPE in reducing AP severity cannot be made. Due to the reporting bias and lack of comparison group, it is difficult to make a firm recommendation for TPE, and the time for initiating the procedure should be highly individualized. Considering that TPE is a high cost procedure with risk, which patients will most likely benefit from and be best suitable for TPE must be a study priority in the future. Better designed prospective and large-scale studies are needed to provide empiric data and a definitive conclusion on the role of TPE as well as to develop guidelines about the adequate timing for commencing therapy in HLAP.

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