URGENT INDICATIONS FOR THERAPEUTIC APHERESIS

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OBJECTIVES

- *It is very important that plasma exchange is not used as a heroic treatment when "there is nothing left to offer".*

Blood Transfus 2011;9:356-61

TPE CLASSIFICATION

- *TPE procedures classified into **3 distinct groups** based on urgency:*
- *1. **Emergent:** TPE shall be started as soon as possible, possibly within 4–6 h from the request*
- *2. **Urgent:** TPE can be initiated within 24 h from the request*
- *3. **Routine:** TPE can be performed during regular working hours based on our clinical practices*

Table 2. ASFA category descriptions[4]

Category	Description
I	Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment
II	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment
III	Optimum role of apheresis therapy is not established; decision making should be individualised
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful; Institutional Review Board approval is desirable if apheresis treatment is undertaken in these circumstances

Table 3. ASFA grading recommendations[4]

Recommendation	Description	Methodological Quality of Supporting Evidence	Implications
Grade 1A	Strong recommendation, high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1B	Strong recommendation, moderate-quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1C	Strong recommendation, low-quality or very low-quality evidence	Observational studies or case series	Strong recommendation but may change when higher-quality evidence becomes available
Grade 2A	Weak recommendation, high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2B	Weak recommendation, moderate-quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2C	Weak recommendation, low-quality or very low-quality evidence	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

RCT, randomised controlled trial. Adopted from Guyatt, 2006; 2008.

Brief review of the technical aspects

- TPE procedures can be performed by either **centrifugation** or **membrane filtration** methods

- The type of **anticoagulant** used depends on the apheresis device, with most devices using citrate

Brief review of the technical aspects

- The **time interval between procedures** is generally based on:
- - the patient's disease
- - the time required to allow the component of interest (e.g. IgG) to re-equilibrate in the intravascular space
- - the need to minimize the risk of bleeding as a result of depletion of coagulation factors, particularly fibrinogen.

Brief review of the technical aspects

- A **1 to 1.5-plasma volume exchange** removes 60–70% of any substance in the intravascular compartment
- Treating volumes in excess of a 1.5-plasma volume exchange confers little benefit
- The most common replacement fluid utilized for TPE is 5% albumin

- The use of **plasma** as a replacement fluid is typically reserved for the treatment **thrombotic thrombocytopenic purpura**

Emergent indications for TPE

- The majority are for **critically-ill patients** (often in the setting of life-threatening disorders)
- TPE should be initiated within 4–6 h from the request (if possible)
- TPE can quickly remove the substance(s) that mitigates the pathogenesis of the disease

Emergent indications for TPE

- TPE may function as a **bridging therapy** prior to the definitive treatment(s)

- These procedures are often performed in an **ICU** as a result of the patient's critical clinical status.

Urgent indications for TPE

- The majority of the patients in this group are acutely, but not critically ill.

- The urgency of TPE is predicated by the patient's clinical symptoms/presentation (i.e. the presence or absence of diffuse alveolar hemorrhage [DAH]).

- If resources can be mobilized, TPE can be initiated quickly.

WHEN to carry out urgent TPE?

- ***For TPE to be effective:***
- *- the clinical picture must be related to a high plasma concentration of a pathogenic substance*
- *- rapid elimination of a pathogenic substance can halt the evolution of the disease*
- *- there must not be valid therapeutic alternatives and*
- *- the severity of the patient's conditions does not allow time to wait for a response to pharmacological therapy*

Blood Transfus 2011;9:356-61

Table 1
Indications for Urgent Plasma Exchange.

Pathology	Category	Grade of Recommendation
Thrombotic thrombocytopenic purpura (TTP)	I	1A
Catastrophic Antiphospholipid Syndrome	II	2C
Acute pancreatitis due to hypertriglyceridemia (HTG)	III	1B
Drug intoxication or poisoning	II/III	2C
Hyperviscosity syndromes	I	1B
Acute fulminant hepatitis	III	2B
Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré Syndrome, GBS)	I	1A
Myasthenia gravis (MG)	I	1A
Neuromyelitis Optica-Spectrum Disease (NMO-SD)	II	1B
Thyroid storm	III	2C

Adapted from Russi et al. [3].

Transfus Apher Sci. 2020 Dec;59(6):102991.

Thrombotic thrombocytopenic purpura (TTP)

- *TPE should be initiated **emergently** once the diagnosis is suspected. If TPE is not immediately available, large dose plasma infusions (25-30 mL/kg), should be given if tolerated, until TPE can be initiated.*

- *TPE is generally performed **daily** until the platelet count is >150 x10^9/L, and LDH is near normal for 2 to 3 consecutive days.*

- *Corticosteroids should be used as an adjunct, either a daily prednisone dose at 1 mg/kg/day, pulsed methylprednisone for a few days, or a combination.*

- *Rituximab, caplacizumab as adjunctive agent.*

Connely-Smith L, et al. J Clin Apher.2023; 38(2):77-278

Catastrophic antiphospholipid syndrome

- Incidence: 5 cases per 10,000,000 persons per year; **Category I Grade 2C;**
- Acquired hypercoagulable state (one or more episodes of venous and/or arterial thrombosis and/or obstetric complications)
- Defined as the acute onset of multiple thromboses in at least 3 organ systems over a period of days or weeks, in patients with antiphospholipid antibodies *(lupus anticoagulant (LA) or persistent antiphospholipid antibodies such as anticardiolipin (aCL) and/or anti-β2-glycoprotein I (anti-β2GPI)*.
- ***Triple therapy*** *approach of* ***anticoagulation*** *plus* ***corticosteroids*** *plus* ***TPE and/or IVIG*** *is the recommended approach to therapy*
- *Daily or every other day TPE for a minimum of 3 to 5 days up to courses of 1-3 weeks*

Connely-Smith L, et al. J Clin Apher. 2023; 38(2):77-278

Acute pacreatititis due to hypertriglyceridemia

- *Incidence: 18/100,000/year;* Category III Grade 1C;
- *HTG-AP have a more severe course than AP due to other causes, with mortality up to 30%.*
- *HTG-AP is associated with TG levels >1,000 mg/dL (>11.3 mmol/L).*
- *A single TPE can reduce TG levels 49-97%.*
- *Treatment goals: reduce TG levels to 500-1000 mg/dL (5.6 mmol-11.3 mmol/L).*
- **Indication for TPE**: patients with HTGP (serum triglyceride level >1000 mg/dL plus lipase >3 times the upper limit of normal) **and** worrisome features (hypocalcemia, lactic acidosis, signs of worsening systemic inflammation or organ dysfunction, and/or multi-organ failure)
- *Frequency: Daily for 1 to 3 days depending upon patient course and TG level;*

Connely-Smith L, et al. J Clin Apher. 2023; 38(2):77-278
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Hyperviscosity syndromes

- *Incidence: 5/1,000,000/year;* Category I Grade 1B;
- *Seen in 10-30% of patients with Waldenström's macroglobulinemia associated with monoclonal IgM*
- *An **early HVS diagnosis** is crucial to prevent further progression and can usually be made from the fundoscopic exam.*
- *TPE reduces viscosity 20-30% per treatment.*
- Duration of TPE: *Daily or every other day TPE until acute symptoms abate (generally 1-3 procedures).*
- *Systemic chemotherapy or immunotherapy should be initiated soon after TPE.*

Connely-Smith L, et al. J Clin Apher. 2023; 38(2):77-278

Acute liver failure

- *Incidence: <10/1,000,000/year;* Category I Grade 1A;
- *The most common causes are acetaminophen toxicity and viral hepatitis.*
- *The mortality rate is 50-90% due to acute metabolic disturbances, hepatic encephalopathy, and severe coagulopathy resulting in multiple organ failure.*
- *TPE can remove albumin bound toxins as well as unbound toxins, including aromatic amino acids, ammonia, endotoxin, indols, mercaptans, phenols, and other factors.*
- *Daily TPE is typically performed for a defined period as a bridge to liver transplantation or liver self-regeneration.*

Connely-Smith L, et al. J Clin Apher. 2023; 38(2):77-278

URGENT TPE IN NEUROLOGY

- Guillain Barre syndrome
- Myastenia gravis
- Neuromyelitis optica spectrum disorders (NMO-SD)

Saheb S, Gallo A. Transfus Apher Sci. 2020; 59(6): 102991

Guillain Barre syndrome

- *Incidence: 1 to 2/100,000/year;* Category I Grade 1A;
- *An acute, typically symmetrical and ascending paralyzing disorder caused by inflammation of the peripheral nerves*
- *Progressive paralyzing illness affecting both motor and sensory peripheral nerves*

- *The typical TPE strategy is to exchange 1 to 1.5 plasma volumes 5-6 times over 10 to 14 days*

Myastenia gravis

- *Incidence: 7 to 23/million;* Category I Grade 1B;
- *Is an autoimmune disease in which antibodies bind to acetylcholine receptors (AChR) at the neuromuscular junction and in skeletal muscle.*
- *The antibodies induce fluctuating weakness of skeletal muscles, which typically worsens later in the day, after repetitive muscle use, or after exercise.*
- *MG can be generalized or localized, and usually involves the eye muscles, causing diplopia and ptosis.*
- ***Myasthenic crisis:*** *a serious, life-threatening event (mortality 5-10%), rapid worsening of MG and airway compromise from ventilatory or bulbar dysfunction, requiring mechanical on non-invasive ventilation.*
- *Major treatment approaches include anticholinesterase inhibitors, thymectomy, immunosuppression, and either TPE or IVIG as rapid but short-acting immunomodulating therapy.*

Myastenia gravis

- *TPE provides immediate intravascular reduction of autoantibody concentration and thus, may provide immediate benefits within hours. However, the effects typically last only 3 to 6 weeks.*
- *For sustained control of MG activity, concomitant immunosuppression must be initiated or modified.*
- ***Apheresis indications:** myasthenic crisis, acute MG exacerbation (particularly in patients with bulbar or severe generalized symptoms) and pre-thymectomy clinical stabilization.*
- *IVIG and TPE are generally regarded as equally effective in treating acute MG.*
- *Frequency: Acute attack/relapse or unstable disease activity: 3 to 6 treatments over 10 to 14 days; weekly to bi-weekly individually adjusted for chronic treatment*

Neuromyelitis optica spectrum disorders (NMO-SD)

- Acute exacerbation of NMO-SD is a medical urgency.
- The standard treatment is high doses of steroids administered intravenously, at a rate of 1 g per day for 3–5 or even up to 10 days in the most severe cases, followed by oral treatment.
- TPEs represent a second-line "rescue therapy" in cases of lack of response to steroid treatment.

Saheb S, Gallo A. Transfus Apher Sci. 2020; 59(6): 102991

Neuromyelitis optica spectrum disorders (NMO-SD)

- Early initiation of TPE (≤ 5 days after symptom onset) is recommended.
- Steroids should preferably be infused at the end of each TPE session.
- For every day of delay in therapy initiation, the chances of achieving complete remission are reduced.
- 1.5 volumes of plasma for five treatments over 10 days.
- The substitute solution is 5% albumin.

Saheb S, Gallo A. Transfus Apher Sci. 2020; 59(6): 102991

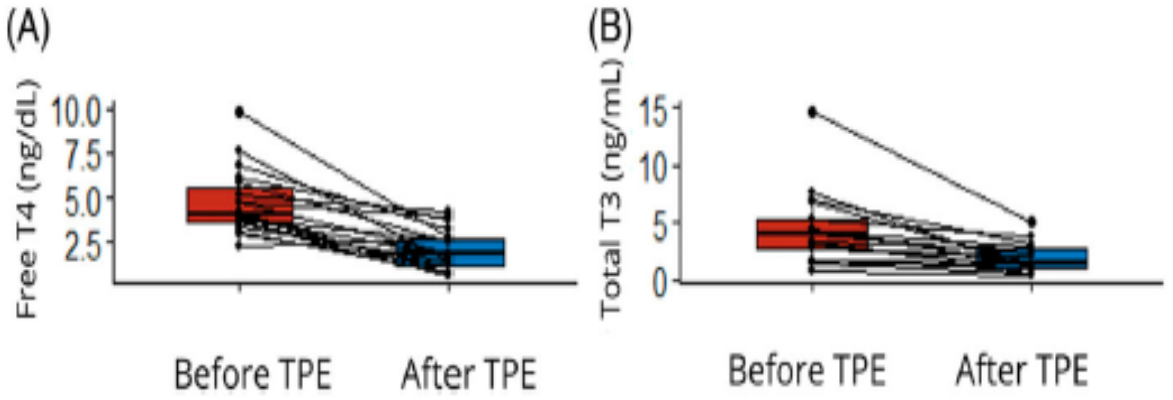
URGENT TPE IN ENDOCRINOLOGY

- ***Thyroid storm and severe thyrotoxicosis*** *remain among the most frequent endocrine emergencies*

- TPE *first reported in 1970 to treat three patients with thyroid storm*
- *TPE is treatment option for:*
- *- patients with thyrotoxicosis and thyroid storm*
- *- inadequate response to medical treatment*
- *- contraindications to therapy or severe side effects*
- *- preparing patients for life-saving thyroidectomy*

URGENT TPE IN ENDOCRINOLOGY

FIGURE 1 Thyroid hormone concentration before and after TPE



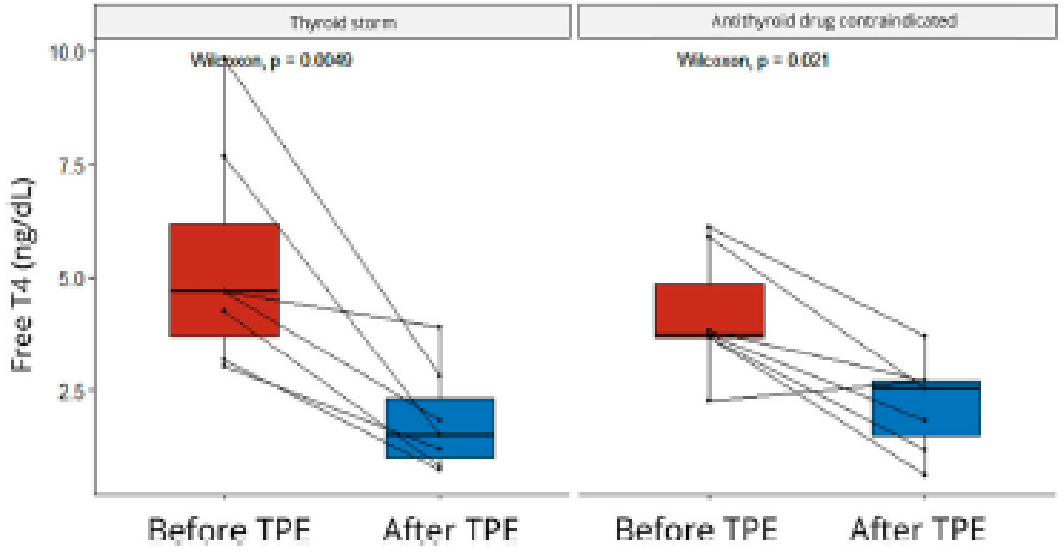


FIGURE 2 Free T4 hormone concentration before and after TPE between treatment indications

-multicenter, retrospective study 2012-2020
-two centers in Colombia
-19 patients
- main indication: thyroid storm and contraindication for antythyroid drugs

Builes-Montano CE, et al. *J Clin Apher. 2021;36:759–65.*

CONCLUSION

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- TPE represent a rescue and preventive therapeutic option in hemodynamically stable patients in an emergency setting.
- Urgency should not obscure the clinical and hemodynamic condition of the patient.
- Fundamental is that the apheresis expert personally assesses the patient and the clinical documentation.
- TPE are undeniably effective when their use is part of a well-defined therapeutic strategy.

THANK YOU FOR ATTENTION.