*Review Articles*

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# Therapeutic Plasma Exchange in Children: A Preliminary Review

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**Abstract**

Therapeutic plasma exchange (TPE) has been a key immunotherapeutic strategy in numerous neurological syndromes, predominantly during the acute phase of illness.The rarity of these immunological disorders in children, combined with a lack of understanding of their pathobiology, has hampered the creation of a solid scientific rationale for TPE therapy and the practicality of larger controlled studies. TPE is still used, but it's a pricey treatment with a lot of side effects. Uncertainty persists over how to compare the various TPE procedures, the best therapeutic dosage, and TPE monitoring and integration with other immunotherapies.

The extracellular component of blood (plasma) is extracted from the cellular component (plasmapheresis), replaced with a colloid or crystalloid substitute, reintegrated with the cellular component, and returned to the patient in therapeutic plasma exchange (TPE). The goal of treatment is to get rid of potential illness mediators such toxic macromolecules and pathogenic autoantibodies from the body.

The method was first described in the early twentieth century, and by the early 1970s, it was widely available for therapeutic application. Since then, the list of therapy indications has grown dramatically, with neurological diseases accounting for a sizable share. However, only 13.4 percent of children admitted for category I (first-line) American Society for Apheresis (ASFA) indications and 9.3 percent of those admitted for category II (second-line) indications received TPE, according to a recent survey of 42 North American Paediatric hospitals that provide the treatment.

**Keywords:** Therapeutic Plasma Exchange; Total plasma volume; Neurological conditions; Central Nervous system; Central Venous Catheter.

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## INTRODUCTION

TPE is a procedure in which a patient's blood is sent through an apheresis machine, where the filtered plasma is extracted and discarded, and red blood cells and replacement fluid such as plasma or albumin are reinfused into the patient.

Over the course of several hours, 1 to 2 total plasma volume (TPV) equivalents around 40 to 80mL/kg, depending on haematocrit are replenished in each exchange. The exponential decay function TPV is used to model the fraction of original plasma (and

thus plasma components of interest in disease) that remains in the intravascular compartment after a single exchange, with 1 TPV removing 63.2 percent of the original plasma, 1.5 TPV removing 77.7%, and 2 TPV removing 86.5 percent.

However, only around 30% of a typical immunoglobulin-G-class autoantibody's total amount in the body is found in the intravascular space, with the balance being in the tissues and interstitial fluid (third space). Multiple exchanges are thus required; after each exchange, a concentration gradient between the extravascular and intravascular compartments is established; the time between exchanges allows pathogenic molecules to equilibrate across compartments (tissue to serum, and especially cerebrospinal fluid to serum), often but not always along the concentration gradient established during the exchange, resulting in more effective clearance in subsequent exchanges.

TPE can clearly reduce circulation levels of autoantibodies and other immunogenic proteins by a significant (although transitory) amount (immune complexes, proinflammatory cytokines, complement). As a result, in disorders of the peripheral nervous system where blood-borne autoreactive disease mediators have direct access to their nervous system targets, TPE's mechanism of action is well characterised, even if the exact disease mediators for some conditions are unknown (e.g., chronic inflammatory demyelinating polyradiculoneuropathy).

### *Practical and Technical Considerations in Children*

Safe and effective plasma exchange in children requires modification of adult protocols to take into account differences in size and physiology. With the appropriate modifications and monitoring, TPE can be undertaken on children of any age and weight; an international survey found 40% of centres treated patients less than 12 months old, and 36% had no lower weight limit for undertaking apheresis.

The three main methods of apheresis are in children, continuous centrifugation (in which blood is removed and replaced simultaneously) is generally considered preferable to intermittent centrifugation (in which blood is removed in batches, which are separated and reconstituted individually before replacement). Membrane filtration is most commonly used in renal units.

## PREPARATION FOR TREATMENT

The usual (although not mandatory) setting for treatment is the intensive care or high dependency unit. Personal protective equipment should be used for all patients and isolation if necessary. A central venous catheter (CVC) is not essential for centrifugal TPE, but is often used owing to difficulty in obtaining and maintaining large bore peripheral access, especially in smaller children. If a CVC is required, the internal jugular vein is usually preferred; femoral catheters limit mobility and may pose a greater infection risk; subclavian catheters are more prone to obstruction and displacement. Tunnelled lines are preferred over temporary ones, especially if a prolonged course of treatment is anticipated. Very rarely, surgically inserted vascular ports have been used in children anticipated to require long term TPE. It is our practice to defer starting TPE for 24 hours after any surgical procedure, including line insertion, to minimize the risks of bleeding and cardiovascular instability.

Laboratory parameters including serum albumin, calcium, renal function, full blood count, clotting profile, and blood group should be checked at baseline and serum stored for future tests, as circulating levels of, for example, autoantibodies are expected to be significantly reduced during and after a course of treatment. Serum should also be tested for blood borne infections such as human immunodeficiency virus and hepatitis B and C, to document any pre treatment exposure.

Premedication with paracetamol and antihistamine reduces the risk of mild transfusion related reactions such as urticaria, and low grade fever and chills, which are commonly reported during TPE. If there is a history of previous transfusion reaction, corticosteroids might also be used.

Blood held in the equipment during exchange (extracorporeal volume, typically 160–185mL in a continuous centrifugation circuit) may represent a significant proportion of total blood volume in smaller children; extracorporeal volumes up to 8% to 10% of total blood volume are generally acceptable, with an absolute maximum of 15%. In smaller children the circuit is therefore primed with packed red cells, or volume expanders in non-anaemic patients, to ensure a neutral or positive fluid balance when exchange begins. The exchange is not started until baseline observations (heart rate, blood pressure, respiratory rate, oxygen saturations, and core and peripheral temperatures)

are stable and the full blood flow rate is established.

## ADMINISTRATION OF TREATMENT

The volume of plasma exchanged in a single session is typically 1, 1.5, or 2 times the patient's TPV, up to a maximum of 4L. The first session is usually limited to a single (1×) TPV exchange of, for example, 50mL/kg, depending on haematocrit (TPV=[0.065×weight] × [1−haematocrit]). plasma removed during TPE is replaced with a substitute fluid, typically 5% albumin. The albumin concentration in the replacement fluid should differ by no more than 10g/L from the child's serum albumin; dilution of 5% albumin with 0.9% saline is often required. Rates of removal and replacement must be monitored, recorded, and balanced to prevent cardiovascular instability; blood pressure and other vital signs should be closely monitored at 15 to 30 minute intervals throughout the exchange, and urine output should be measured.

Citrate or heparin are added to the exchange circuit to prevent blood clotting within the equipment. Citrate produces its anticoagulant effect by chelation of ionized calcium; it is rapidly cleared in the body in patients with normal hepatic and renal function and causes minimal systemic anticoagulation, but commonly causes hypocalcaemia. Calcium is usually added continuously to the circuit after filtration to counteract this. Citrate is generally preferred to heparin, which confers a greater risk of bleeding. Coagulopathy may also result from depletion of clotting factors; fresh frozen plasma is usually included in the replacement fluid if a daily schedule of exchanges is planned, or if the fibrinogen level pre-exchange is less than 100 to 140mg/dL.7, Some centres also advocate fresh frozen plasma supplementation for patients undergoing TPE within 48 hours of surgical procedures, including CVC insertion.[9]

Laboratory parameters should be rechecked after each procedure during the exchange period, or more frequently if corrections are required. Invasive procedures should be avoided for 4 to 6 hours after exchange owing to the risk of bleeding.

## CONCLUSIONS

There is an emerging consensus for earlier initiation of immunotherapy in autoimmune neurological disorders., There is evidence of improved outcome in children diagnosed and treated early in several disorders including acute disseminated encephalomyelitis, and anti-NMDAR encephalitis.

TPE has an important role in the first line immunotherapy of these conditions. It offers direct and immediate removal of pathogenic autoantibodies and other disease mediators from the periphery, with immunomodulatory effects on the CNS also, especially when combined with immunosuppressive treatment. The evidence base supporting its use continues to expand.

The principal reservations about TPE are the demands of administering it and its high complication rate. However, many of the reported complications become apparent only because patients are aggressively monitored; they are usually minor, and either self limiting or easily correctable; many can be prevented by routine administration of calcium and close attention to cardiovascular status.

Although TPE is a powerful tool in the acute stabilization of severe neuroimmunology disorders, it is unlikely to modify the underlying disease process and clinical trajectory in most conditions. TPE and other first line immunotherapies should not therefore delay escalation to second-line disease modifying therapies where these are indicated.

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