

# Therapeutic plasma exchange in paediatric neurology: a review and proposed treatment algorithm

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## **ABSTRACT**

Therapeutic plasma exchange (TPE) has been the key immunotherapeutic strategy in numerous neurological syndromes, predominantly during the acute phase of illness. This article reviews the indications, strength of evidence and safety of TPE in children with neurological conditions. The rarity of these immune conditions in children, alongside an often incomplete understanding of their pathobiology, has limited the development of a robust scientific rationale for TPE therapy and the feasibility of conducting larger controlled trials. TPE continues to be utilised, but is a costly therapy with common adverse effects. Uncertainty remains over how to compare the different TPE methods, the optimal dosage of therapy, monitoring and integration of TPE with other immunotherapies. Further studies are also required to define the indications and benefits of TPE and assess evolving technologies such as immunoabsorption.

### **What this paper adds**

- Small and mainly uncontrolled studies provide evidence for the efficacy of therapeutic plasma exchange (TPE) in childhood neuro-inflammatory conditions.
- TPE is generally well-tolerated provided key adverse effects, such as hypocalcaemia, are anticipated and avoided.
- There needs to be careful consideration into evaluating how TPE can be systematically dosed and outcomes objectively assessed.

## INTRODUCTION

In therapeutic plasma exchange (TPE) the extracellular component of blood (plasma) is separated from the cellular component (plasmapheresis), replaced with a colloid or crystalloid substitute, reintegrated with the cellular component, and returned to the patient. The aim of treatment is to remove from the body putative disease mediators such as toxic macromolecules and pathogenic autoantibodies (1).

The procedure was first described in the early twentieth century (2) and became widely available for clinical use in the early 1970s. Since then the range of indications for treatment has expanded significantly, with neurological conditions comprising a large proportion (3). However the uptake of TPE in children remains limited; in a recent survey of 42 North American paediatric hospitals providing TPE, the treatment was used in only 13.4% of children admitted for category I (first-line) American Society for Apheresis (ASFA) indications, and only 9.3% of those admitted for category II (second-line) indications (4).

In this article we provide an overview of the theoretical basis for TPE in neurological diseases of the central and peripheral nervous system, review the indications and evidence for TPE in those diseases affecting children, and discuss the practical, technical, safety and tolerability issues to be considered when embarking upon TPE in children, and its use alongside other immune therapies. We also offer a proposed algorithm to guide decision-making around initiation of TPE in children with neurological conditions (Figure 1) (5, 6).

## THEORETICAL BASIS FOR PLASMA EXCHANGE

A course of TPE typically comprises 3-5 or more separate exchange procedures undertaken at 24-48 hourly intervals. The rationale for this is determined by the removal kinetics of the exchange process (see Figure 2).

In each exchange 1-2 total plasma volume (TPV) equivalents – roughly 40-80mL/kg, depending on haematocrit – are replaced over a period of several hours. The fraction of original plasma (and therefore plasma components of interest in disease) remaining in the intravascular compartment after a single exchange is modelled by the exponential decay function  $e^{-TPV}$ , such that removal of 1 TPV removes 63.2% of the original plasma, 1.5 TPV removes 77.7%, and 2 TPV removes 86.5%.

However, for a typical IgG-class autoantibody, only around 30% of the total amount in the body is located in the intravascular space, the rest residing in the tissues and interstitial fluid (third space) (7). Multiple exchanges are therefore required – after each exchange a concentration gradient is established between the extra- and intravascular compartments; the interval between exchanges allows time for equilibration of pathogenic molecules across compartments (tissue to serum, and importantly CSF to serum), often but not invariably along the concentration gradient established during the exchange, resulting in more effective clearance in subsequent exchanges.

Additional considerations specific to the pathogenic molecule include its rate of ongoing synthesis and catabolism, volume of distribution, and rate of equilibration between bodily compartments, which may be as slow as 1-3% per hour for large molecules (8). For example, IgG and IgA distribute

more extensively in the extravascular space than IgM due to their lower molecular weight; hence they re-accumulate in the plasma more readily after each exchange and require a larger number of exchanges to achieve the same clearance (9). The targeted cumulative effect of a course of exchanges is to remove up to 90% of the total body burden of pathogen (8).

### **Additional considerations in neurological disease**

It is clear that TPE can effect substantial (if transient) reductions in circulating levels of autoantibodies and other immunogenic proteins (immune complexes, pro-inflammatory cytokines, complement). Therefore in diseases of the peripheral nervous system (PNS), in which blood-borne autoreactive disease mediators have direct access to their nervous system targets, the mechanism of action for TPE is readily understood, even if the specific disease mediators are not fully known for some conditions (e.g. chronic inflammatory demyelinating polyradiculoneuropathy).

In diseases of the central nervous system (CNS), although the efficacy of TPE is established for a range of conditions, the mechanisms of action are less clear. However several key observations about the origins of aberrant autoimmune response in the CNS provide insights into some of the potential immunotherapeutic effects of TPE:

1. In health, the CNS is largely isolated from blood-borne disease mediators by the blood-brain barrier (BBB), which regulates the movements of biomolecules between the periphery and CNS at all levels of the cerebrovascular tree (reviewed in Obermeier et al., 2016 (10)). BBB disruption is observed in many acute disorders of the CNS (e.g. acute disseminated encephalomyelitis), manifest as gadolinium enhancement on neuroimaging. In this state of compromised barrier integrity, blood-to-brain trafficking of immune cells and inflammatory mediators is greatly increased, and TPE (especially when initiated earlier in the disease course) may be able to attenuate this. This is supported by the finding that presence of ring-enhancing lesions on neuroimaging is associated with greater benefit from TPE in steroid-refractory CNS inflammatory demyelinating disease, independent of the cause (11).
2. Immune cross-talk is prevalent between the periphery and CNS: various pro-inflammatory cytokines are selectively shuttled from blood to brain via active transcellular receptor-dependent mechanisms; and some brain regions (e.g. periventricularly) permit limited passive exchange of immune mediators via loosely-sealed gaps between endothelial cells (12). In clearing these mediators from the periphery, TPE could modulate autoreactive immune activity within the CNS.
3. As in most antibody-mediated CNS diseases autoimmune induction is thought to occur outside of the CNS, removal of antibodies from circulation would reduce the antibody load gaining access to the CNS via diffusion across a healthy/temporarily breached BBB. However this may be significantly less effective when antibody-producing plasma cells have gained access to the CNS and are producing antibodies intrathecally.

As such, TPE may be theoretically effective in CNS disease when there is severe or fulminant inflammation in the brain (and spine), particularly when systemic inflammation may also feature and act to drive central inflammation.

## NEUROLOGICAL INDICATIONS FOR PLASMA EXCHANGE

The American Society for Apheresis (ASFA) and American Academy of Neurology (AAN) publish evidence-based recommendations on indications for therapeutic apheresis; those of greatest relevance to paediatric neurologists are summarised in Table 1 (13, 14). The ASFA make strong recommendations for a first-line role for TPE in the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), Guillain-Barré syndrome, myasthenia gravis (moderate-severe crisis/preoperative), and N-methyl-D-aspartate receptor (NMDAR) antibody encephalitis; and weaker or second-line recommendations for TPE in acute disseminated encephalomyelitis (ADEM), limbic encephalitis, multiple sclerosis, neuromyelitis optica spectrum disorders and paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). The ASFA has also issued recommendations on TPE for other neurological conditions including Hashimoto's encephalopathy, paraneoplastic encephalitis, Rasmussen encephalitis, stiff person syndrome and Sydenham's chorea (13); and TPE has been used 'off-label' to treat Bickerstaff's brainstem encephalitis (15), opsoclonus-myoclonus syndrome (16), optic neuritis (17), transverse myelitis (15), and neurological manifestations of systemic autoinflammatory diseases (reviewed in Kampylafka et al., 2016 (18)).

Also provided in Table 1 are summaries of the role and evidence specific to children with these conditions (the ASFA and AAN recommendations do not discriminate children from adults) (11, 13-15, 19-72). We have also provided a more detailed review of this literature in the supplemental materials.

## 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 <12 months old, and 36% had no lower weight limit for undertaking apheresis (73).

The three main methods of apheresis are compared in Table 2 (7-9). 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 (though 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 (see Table 2), but is often utilised due 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 (9). Tunneled lines are preferred over temporary lines, 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 (74). It is our practice to defer commencing TPE for 24 hours after any surgical procedure, including line insertion, to minimise 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 e.g. 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 HIV 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, low grade fever and chills (7), which are commonly reported during TPE (75). If there is a history of previous transfusion reaction corticosteroids might also be used (9).

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 (TBV) in smaller children; extracorporeal volumes up to 8-10% of TBV are generally acceptable, with an absolute maximum of 15% (9). 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 commenced until baseline observations (heart rate, blood pressure, respiratory rate, oxygen saturations, core and peripheral temperature) 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 x the patient's total plasma volume (TPV), up to a maximum of 4 litres. The first session is usually limited to a single (1 x) TPV exchange of e.g. 50mL/kg, depending on haematocrit ( $TPV = [0.065 \times \text{weight}] \times [1 - \text{haematocrit}]$ ) (9). 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 15-30 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 ionised 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 post-filtration to counteract this (7, 32, 66). Citrate is generally preferred to heparin, which confers a greater bleeding risk (76). Coagulopathy may also result from depletion of clotting factors; fresh frozen plasma (FFP) is usually included in the replacement fluid if a daily schedule of exchanges is planned, or if the fibrinogen level pre-exchange is <100-140 mg/dL (7, 66, 77). Some centres also advocate FFP supplementation for patients undergoing TPE within 48h of surgical procedures, including CVC insertion (9).

Laboratory parameters should be rechecked following each procedure during the exchange period, or more frequently if corrections are required. Invasive procedures should be avoided for 4-6h post-exchange due to bleeding risk (8).

### **Tolerability**

In our experience TPE is usually well tolerated in children who are able to cooperate. In one cohort the rate of anxiety or lack of cooperation was only 1.4% per procedure (78). During each procedure the child is effectively bedbound, although in most cases mobility is limited anyway by the underlying condition. Younger children may find the procedure uncomfortable and struggle to stay still. Involvement of a play specialist or, failing this, oral sedation can help. Treatment is particularly challenging in those with prominent movement disorders, e.g. in anti-NMDAR encephalitis; sedation with general anaesthetic in the intensive care setting may be required in such cases.

## **COMPLICATIONS**

TPE is an invasive procedure with common adverse effects, occurring up to twice as frequently in children compared to adults, although these are usually mild and correctable. Table 3 summarises reported complication rates in the larger paediatric cohorts (32, 79-82). Some of the variability between studies is due to differing thresholds for definition of complications, and some is due to differences in patient populations.

### **Potentially life-threatening complications**

In Michon et al. there were two deaths (1% of patients) (78). One was due to coronary thrombosis in a patient with multiorgan failure secondary to thrombotic thrombocytopenic purpura, and one was due to haemorrhage related to anticoagulation therapy for suspected pulmonary embolism, in a patient with sickle cell disease and disseminated intravascular coagulation; i.e. the deaths occurred in patients undergoing apheresis for systemic haematological problems, and were not clearly attributable to the apheresis itself. There also occurred in this cohort one case of malignant arrhythmia due to citrate toxicity (caused by a misplacement of the infusion line), and four cases of angioedema or anaphylactic shock after blood product infusion. It should be noted that this cohort included children undergoing apheresis for non-neurological indications, who may have had a higher requirement for blood products than the paediatric neurology population. Of two studies of exclusively paediatric neurology cohorts conducted in high-resource settings, there were no life-threatening complications (81, 82). The incidence of death associated with TPE in a meta-analysis of 15,658 (mostly adult) cases was 0.05% (83).

### **Complications of central venous access**

General anaesthetic is required for CVC insertion in younger children, which is not without risks, especially in those with autonomic dysfunction e.g. due to Guillain-Barré syndrome or anti-NMDAR encephalitis. CVC insertion is usually performed by interventional radiology under direct visualisation. Post-insertion complications include line obstruction by thrombosis, accidental line displacement, and line infection. Central line bacteraemia was detected in 16% of children in one series (78), but clinically significant infection associated with TPE is unusual, even in patients on

immunosuppressive therapies; in a randomised-controlled trial of 86 adults with severe lupus nephritis there was no difference in infection rate between those receiving immunosuppression (high-dose steroid and cyclophosphamide) plus TPE, and those receiving immunosuppression alone (84).

### **Depletion of nonpathogenic blood components**

Plasmapheresis is a nonselective process in which pathogenic and useful substances alike are removed from circulation. In removing 1-2g of pathogenic substance from the body up to 110g of albumin and 40g of immunoglobulin may also be removed. Levels of immunoglobulin take an average 35 days to return to baseline after TPE in adults. Coagulation factors (particularly fibrinogen) are also depleted, with up to 30% increase in prothrombin time and 100% increase in thromboplastin time after a single exchange. Endogenous production typically leads to self-correction of prothrombin and partial thromboplastin times within 24-48h, and fibrinogen level within 72h (85); however supplementation is often required.

A degree of red cell anaemia is quite common, especially if the circuit is unprimed or there is haemolysis due to e.g. kinks in the circuit tubing, hypo-oncotic albumin or use of the membrane filtration method. Thrombocytopenia is also common, but tends to self-correct within 24h in adults (85). Risk is higher if heparin-based anticoagulation is used.

### **Electrolyte derangements**

Hypocalcaemia due to citrate toxicity is a common complication of TPE. Early symptoms include mild dysaesthesias, nausea and vomiting, abdominal pain, headaches and dizziness. Younger children are often unable to report these; frequent monitoring of pre- and post-treatment ionised calcium is therefore recommended to maintain levels >1.0 mmol/L. More severe effects including tetany, cardiac arrhythmias and seizures are also reported in association with TPE (76), especially at ionised calcium <0.8 mmol/L. If FFP is included in the replacement fluid the citrate load is increased further. Citrate and heparin can be used in combination to reduce citrate load if necessary.

Other consequences of citrate toxicity include hypomagnesaemia, hypokalaemia and metabolic alkalosis due to elevated bicarbonate. The latter further exacerbates hypocalcaemia due to dissociation of H<sup>+</sup> ions from albumin leading to increased calcium binding (8). Use of albumin solution also contributes to hypokalaemia and supplementation is often required.

### **Hypotension**

Hypotension is a common occurrence during paediatric TPE, necessitating intravenous fluid boluses in up to 5% of procedures (78). Even in a primed continuous centrifugation circuit, mismatch between the volume and constituents of the removed plasma and its replacement may result in blood pressure instability. Smaller children are at higher risk as the volume held extracorporeally in the circuit represents a greater proportion of total blood volume. Other risk factors include hypocalcaemia (8), anaemia (78) and autonomic dysfunction associated with e.g. anti-NMDAR encephalitis (86). Concurrent use of neuroleptics for agitation in anti-NMDAR encephalitis may further increase the risk of dysautonomia.

### **Other complications**

Allergic reactions associated with albumin infusion are rare and usually mild (7). FFP can produce more severe reactions including anaphylaxis and transfusion-related acute lung injury (78, 83). As with other pooled blood products, FFP confers a theoretical risk of infection from e.g. unscreened viruses and prion diseases. Hypothermia is not uncommon; a blood warmer is commonly incorporated into the return line, although this adds an additional 20-50mL to the extracorporeal volume (77, 78). Neuropathic pain/paraesthesia has been reported in up to 6% of patients (82).

## **USE ALONGSIDE OTHER THERAPIES**

TPE has a place in the first-line treatment alongside steroids and intravenous immunoglobulin (IVIG) for many conditions in paediatric neurology (see Figure 1). The role of TPE in specific conditions is summarised in Table 1 (with further details in supplemental materials); but some general principles can also be applied.

### **In serial**

In most situations high-dose intravenous corticosteroids are tried before other immunotherapies, due to their ease of administration and generally favourable risk and tolerability profile. In cases where the response to pulse steroid is suboptimal, the question often arises of whether to use IVIG or TPE as rescue first-line therapy. In a few conditions there is evidence favouring the efficacy of one over the other, but more often the decision rests on a balance of ease of administration, safety and tolerability, speed of action and cost (Figure 3) (3, 7, 87, 88).

When planning a sequence of therapies the question arises of the appropriate interval between treatments. In the acute context our practice is to allow 48-72 hours for treatment effect to become apparent before initiating the next therapy; but this interval may be reduced in **fulminant or life-threatening presentations** (Figure 1). It should be noted that IVIG is significantly removed from circulation by TPE; hence a treatment regimen in which TPE immediately follows IVIG should be avoided where possible. There is evidence to support this approach from a study of children treated with TPE and IVIG for anti-NMDAR encephalitis, in which superior response was observed in those treated with TPE followed by IVIG, versus those treated with IVIG followed by TPE (65).

### **In parallel**

There is a compelling rationale for undertaking TPE concurrently with immunosuppressive therapy (i.e. corticosteroids) in CNS disorders characterised by intrathecal antibody production: TPE clears antibodies from the serum and downgrades peripheral immune activation, while steroid acts centrally to modify the intrathecal production. Synergistic effect of TPE and steroids has been observed in conditions such as limbic encephalitis (LE) associated with voltage-gated potassium channel (VGKC) complex autoimmunity (36, 38) and anti-NMDAR encephalitis (58).

Various medications are removed from the body by TPE, especially those with a low volume of distribution and those which are highly protein bound (89). Removal of corticosteroids is minimal, but best practice is to give doses post-exchange where possible. When TPE and IVIG are administered in parallel (with the rationale that IVIG removes from circulation any pathogenic autoantibodies remaining after TPE), timing of therapies should be arranged such that doses of IVIG

are not administered immediately prior to exchange. Rituximab and other monoclonal antibodies are also significantly removed by TPE; exchange should ideally be delayed at least 24-48h after rituximab administration (8).

Non-immunological medications removed by TPE include antibiotics such as cephalosporins and vancomycin, and antiepileptics such as phenytoin and sodium valproate (89). Changes should be made to administration times to avoid dosing immediately prior to exchange; levels should be monitored to ensure plasma concentration is at the higher therapeutic range at the start of each exchange (to minimise risk of subtherapeutic levels during exchange); and supplementary doses may be required after each exchange, guided by trough levels (9, 40, 89).

## **CONCLUSIONS**

There is an emerging consensus for earlier initiation of immunotherapy in autoimmune neurological disorders (90, 91). There is evidence of improved outcome in children diagnosed and treated early in several disorders including ADEM (27, 28) and anti-NMDAR encephalitis (58, 92).

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 regarding 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 stabilisation of severe neuroimmunological 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.

## **PRIORITIES FOR FUTURE RESEARCH**

- Promotion of early recognition and diagnosis of neuroimmunological conditions in children, so the benefits of early treatment can be maximised.
- Establishment of national treatment registries (as in France and Sweden) for case ascertainment and standardised reporting of adverse effects and outcomes, using validated quantitative measures appropriate to the patient population.
- Standardisation of the technical parameters of TPE in children, including equipment (instruments, circuits, catheters, software), anticoagulation protocols, priming practice,

circuit extracorporeal volume, flow rate and pressures, many of which vary considerably between centres at present (73).

- Prospective studies to establish the role and optimal 'dosing' and scheduling of TPE in the various indications, using objective and quantifiable measures of treatment effect, to address therapeutic questions such as: could TPE be used as induction therapy, rather than rescue therapy, in some children?
- Future advances in the understanding of the molecular basis of neuroimmunological disorders, and faster laboratory turnaround, may facilitate use of e.g. autoantibody levels to guide therapy during courses of TPE.
- There has been a resurgence of interest in immunoadsorption, in which separated plasma is processed to remove a specific pathogenic molecule and returned to the body (i.e. regenerated rather than replaced) (7, 93). In adults immunoadsorption has equivalent efficacy to TPE for myasthenic crises (94) and relapses of MS and NMO (95), with equivalent or superior safety profile. It is hoped that such systems could be more widely used in future.

## TABLES

**Table 1: Indications for therapeutic plasma exchange (TPE) in selected neurological conditions affecting children**

Condition	ASFA recommendation (11)			AAN recommendation (12)		Theoretical rationale for TPE	Role of TPE and supporting evidence in children (see supplemental materials for further details)	Recommended timing and volume of exchanges (see supplemental materials for further details)
	Treatment role	Recommendation strength	Evidence quality <sup>1</sup>	Conclusion	Evidence quality <sup>1</sup>			
Acute disseminated encephalomyelitis/acute transverse myelitis	Second-line	Weak	C	Possibly effective <sup>2</sup>	B	Modulation of an abnormal humoral and cell-mediated immune response directed against CNS oligodendrocytes in the context of an acutely disrupted blood-brain barrier. Anti-MOG antibodies are present in around half of cases (19, 20)	A small RCT found reduced morbidity in adults with ADEM/ATM given TPE (70); there is otherwise a lack of high-quality evidence for acute therapies in adults or children (21, 69). TPE is largely reserved for the severely unwell who fail to respond to high-dose steroid. In children several case series report improvement in ADEM, with most but not all enjoying full recovery (22-26); around half of children with ATM have responded to TPE (26).	ASFA suggests 3-6 alternate-day exchanges of 1-1.5 TPV. Clinical response is usually noticeable within 2-3 days (13). Earlier initiation is associated with a better outcome (27, 28). TPE can be given concurrently with IVIG (29) and/or steroid (69) in children with significant deficits.
Chronic inflammatory demyelinating polyradiculoneuropathy	First-line	Strong	B	Established effective <sup>3</sup>	A	Modulation of an abnormal humoral (pro-inflammatory cytokines) and cell-mediated immune response directed against presumed targets in the peripheral nerve.	Optimal treatment is not clearly defined (30). TPE is used largely as adjuvant therapy for children with severe disease at onset, or after failure of IVIG and steroid. Meta-analysis of 12 studies found only 14% of children receiving TPE as first-line therapy showed a good response, compared to 79% of those treated with IVIG and 84% of those treated with steroid (31).	ASFA suggests 1-1.5 TPV exchanges 2-3 times per week until clinical improvement is achieved, followed by a tapering regimen. Maintenance therapy of exchanges on a weekly to monthly basis may be continued thereafter if required (13).
Guillain-Barré syndrome/acute inflammatory demyelinating polyneuropathy	First-line <sup>4</sup>	Strong	A	Established effective	A	Removal of blood-borne autoantibodies directed against peripheral nerve gangliosides; antibodies correlate with clinicopathological subtypes but are not found in all cases.	Largely used second-line as rescue therapy in IVIG nonresponders; dramatic improvements reported in ten such cases in one study (32). First-line role is supported by a single RCT of TPE versus IVIG in 41 ventilated children with GBS; duration of ventilation was shorter in the TPE group (11 days versus 13 days) but there was no difference in mobility at four weeks (33).	ASFA suggests 5-6 exchanges of 1-1.5 TPV on an alternate day regimen (13). Benefit is greatest when started within the first week of symptoms (34). Additional TPE may be helpful in those relapsing 2-3 weeks after initial treatment (13).
Limbic encephalitis <sup>5</sup>	Second-line	Weak	C	[Not reviewed by AAN]		Removal of likely pathogenic autoantibodies directed against	May be used as rescue therapy in children not responding to first-line immunotherapy but there	ASFA suggests 5-7 exchanges of 1-1.5 TPV over 7-14 days for acute VGKC

					neuronal cell-surface proteins such as those associated with the VGKC complex (e.g. LGI1, contactin-2, CASPR2); antibody titres in some correlate with clinical syndrome (35) and course (36).	is very little evidence to support practice. In one series two children undergoing TPE for antibody-positive limbic encephalitis both showed improvement with treatment, although in one the improvement came only when TPE was combined with high-dose oral steroid (37). TPE has also been used as maintenance therapy in adults.	autoimmunity (13). Concurrent steroids have been used in several studies and may have a synergistic effect (38).	
Multiple sclerosis (acute/relapse)	Second-line	Strong	B	Probably effective	A	Modulation of an abnormal humoral and cell-mediated immune response through incompletely understood mechanisms.	Children with inadequate response to first-line steroid therapy usually respond to IVIG or a second steroid pulse; TPE is very rarely required. However there is international consensus for consideration of TPE as a treatment option in such cases (39), especially in those with fulminant demyelination or significant functional disability (40). Several cases are reported in which TPE was associated with improvement (41-44).	The recommended course of TPE for relapses consists of 5-7 exchanges over 14 days (13, 40). Response rate in adults is around 50%; early initiation of therapy within 14-20 days of onset is associated with greater benefit (13).
Myasthenia gravis (in moderate-severe crisis or as preoperative therapy)	First-line	Strong	B/C <sup>6</sup>	Insufficient evidence	C	Removal of established pathogenic blood-borne autoantibodies directed against postsynaptic targets at the neuromuscular junction (acetylcholine receptor, MuSK receptor, LRP4).	Has been used as short-term therapy for moderate-to-severe bulbar and respiratory crisis, as rescue therapy where other treatments have failed, and for preoperative optimisation (32, 45, 46). Efficacy is not established due to lack of clinical trials (47). Has also been used as maintenance therapy (48).	ASFA suggests daily or alternate-day exchanges for myasthenic crisis, with 1-1.5 TPV or less exchanged per procedure (13). In juvenile MG 8-10 single volume exchanges over two weeks have been used (46). The clinical effect is usually seen within days. May be more effective when initiated earlier in the disease course. Post therapy there is a gradual reduction in effect over 2-4 weeks (13).
Neuromyelitis optica spectrum disorders	Second-line <sup>7</sup>	Strong	B	Possibly effective <sup>2</sup>	B	Removal of established pathogenic blood-borne autoantibodies directed against the astrocyte AQP4 channel (which lies in close contact with the periphery at the blood-brain barrier) and other immunogenic proteins (complement) with established role in the pathogenesis (49). Rationale less clear in the anti-MOG group.	TPE is used as second-line therapy in children with severe symptoms that fail to improve with steroid. Evidence to support this is limited to a small number of cases from the paediatric literature (15, 41, 50, 51) and two larger case series in which some children were included (11, 52). TPE has also been used as maintenance therapy in some patients (53).	A course of five 1-1.5 TPV exchanges is recommended, usually on alternate days (13, 54). 50-70% of patients respond to treatment (11); improvement is usually apparent by the third exchange (55). Early initiation is associated with better outcome; AQP4-IgG status does not appear to influence response (56).
N-methyl-D-aspartate receptor antibody	First-line	Strong	C	[Not reviewed by AAN]		Removal of established pathogenic autoantibodies targeting the NR1	Current treatment protocols, which are based on retrospective studies only, accord TPE a first-	ASFA suggest 5-6 exchanges of 1-1.5 TPV, administered on alternate days to

encephalitis				subunit of the neuronal cell-surface NMDA receptor, titres of which correlate with disease activity (57). Antibodies are found in blood and CSF but are mostly of intrathecal origin.	line role alongside steroid and IVIG. It has been used in over 200 children in the literature, in most cases as rescue therapy in those not responding to steroid and IVIG (58-61). Combination of TPE with steroid is associated with better outcome (60). Children with predominantly psychiatric symptoms appear to benefit more from TPE, while those with a predominantly catatonic presentation benefit less (62). TPE has also been used for treatment of relapses (63) and as second-line therapy for treatment-resistant disease (64).	allow time for equilibration of antibody levels between CSF and serum (13). Early initiation of treatment is associated with better outcome (58). Where IVIG and TPE are used together, superior response is observed in those receiving TPE prior to IVIG (65). Immediate clinical improvement after a course of TPE may be expected in around two thirds of children (58), with peak efficacy around the third to fifth exchange (66). High initial antibody titre is associated with longer time for response to therapy.		
Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (exacerbation <sup>8</sup> )	Second-line	Strong	B	Insufficient evidence	C	Removal of postulated autoantibodies triggered by streptococcal infection and reactive against neuronal targets in the CNS; highly controversial pathogenicity.	TPE may be considered as rescue therapy in severe-to-extreme cases, or first-line in situations of life-threatening functional impairment (71); however the evidence for efficacy is so far inconclusive (72). A small, unblinded RCT found TPE superior to no treatment (67). A retrospective, non-controlled series of 35 cases found average symptom score 65% reduced at six months post treatment with TPE (68).	The ASFA suggests daily or alternate day 1-1.5 TPV exchanges for PANDAS. 3-6 procedures may be performed over 1-2 weeks (13, 68)

AQP4, aquaporin-4. ASFA, American Society for Apheresis. AAN, American Academy of Neurology. CASPR2, contactin-associated protein-2. CNS, central nervous system. IVIG, intravenous immunoglobulin. LGI1, leucine-rich glioma inactivated 1. LRP4, low-density lipoprotein receptor-related protein 4. MOG, myelin oligodendrocyte glycoprotein. MuSK receptor, muscle-specific tyrosine kinase receptor. PANDAS, Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. RCT, randomized controlled trial. TPV, total plasma volume.

1. A, Randomised controlled trial/s without important limitations (or overwhelming evidence from observational studies – ASFA only); B, randomised controlled trial/s with limitations (or exceptionally strong evidence from observational studies – ASFA only); C, observational studies or case series.
2. Included under ‘fulminant demyelinating CNS disease’ by AAN.
3. Indication specified as ‘short-term treatment’ by AAN.
4. TPE as add-on therapy *post-IVIG* in GBS is weakly recommended by ASFA on the basis of quality C evidence.
5. Indication specified as ‘voltage-gated potassium channel autoimmunity’ by ASFA.
6. Quality B evidence for use in moderate-severe crisis; quality C evidence for use as preoperative therapy.
7. Strong recommendation based on quality B evidence as second-line therapy for *acute* NMOSD; weak recommendation based on quality C evidence (treatment role not established) as *maintenance therapy* in NMOSD.
8. Indication specified as ‘acute obsessive-compulsive disorder and tics’ by AAN.

**Table 2: Exchange methods**

	<b>Time per exchange</b>	<b>Minimum vascular access</b>	<b>Anticoagulant used</b>	<b>Advantages</b>	<b>Disadvantages</b>
Continuous centrifugation	<2 hours	2 x large-bore PVC; or Double-lumen CVC	Usually citrate	Automated and efficient calculation of anticoagulation and fluid requirements	High cost: complex equipment requiring experienced technician at bedside throughout the procedure
Intermittent centrifugation	>4 hours	1 x large bore PVC; or Single-lumen CVC	Usually citrate	Portable and relatively simple equipment May be undertaken with single peripheral venous access	Suitable only for larger children (e.g. >30kg) due to the large volume of blood (>225ml) held extracorporeally during processing Longer duration of exchange
Membrane filtration	<2 hours	Double-lumen CVC	Usually heparin	Relatively simple equipment Less requirement for blood products	May lead to complement activation and haemolysis

PVC, peripheral venous catheter. CVC, central venous catheter.

**Table 3: Complications of therapeutic plasma exchange (TPE) in children**

Cohort	Michon et al., 2007 (Montreal) (78)*	Brunetta Gavranic et al., 2016 (Zagreb) (79)	Paglialonga et al., 2015 (Europe, 12 centres) (80)	Haque et al., 2014 (Karachi) (32)	Eyre et al., unpublished (UK, 4 centres) (81)	Agarwal et al., 2018 (Houston) (82)	Pooled
Procedures	1,632	1,530	738	130	693	340	4,524
Patients	186	204	67	28	58	50	593
<b>Any complication</b>							
<i>Per procedure (%)</i>	55%	12%	6.9%	14%	--	--	550/3,491 (16%)
<i>Per patient (%)</i>	82%	--	--	--	66%	28%	205/294 (70%)
<b>Potentially life-threatening complications</b>							
<i>Per procedure (%)</i>	--	--	--	3.8%	0%	0%	5/1,163 (0.4%)
<i>Per patient (%)</i>	3.8%	--	--	--	0%	0%	7/294 (2.4%)
<b>Line infection (bacteraemia)</b>							
<i>Per procedure (%)</i>	2.1%	--	--	--	--	--	34/1,632 (2.1%)
<i>Per patient (%)</i>	16%	--	--	--	19%	--	41/244 (17%)
<b>Line obstruction or displacement</b>							
<i>Per procedure (%)</i>	6.1%	2.9%	1.6%	--	--	--	156/3,900 (4.0%)
<i>Per patient (%)</i>	20%	--	--	--	8.6%	--	42/244 (17%)
<b>Hypotension</b>							
<i>Per procedure (%)</i>	14%	0.8%	1.4%	--	--	--	361/3,900 (9.3%)
<i>Per patient (%)</i>	48%	--	--	36%	10%	6%	108/322 (34%)
<b>Allergic reaction</b>							
<i>Per procedure (%)</i>	6.0%	2.0%	--	--	--	--	129/3,162 (4.0%)
<i>Per patient (%)</i>	24%	--	--	--	--	8%	49/236 (21%)
<b>Hypocalcaemia</b>							
<i>Per procedure (%)</i>	6.6%	--	0.3%	--	--	--	110/2,370 (4.6%)
<i>Per patient (%)</i>	64%	--	--	--	22%	--	132/244 (54%)
<b>Anaemia (Hb &lt; 70)</b>							
<i>Per procedure (%)</i>	1.7%	--	--	--	--	--	28/1,632 (1.7%)
<i>Per patient (%)</i>	48%	--	--	--	17%	--	99/244 (41%)

\*This cohort included children undergoing apheresis for non-neurological indications, such as those with high blood product requirement for systemic haematological problems, and may therefore not be representative of the risk in the paediatric neurology population.

## FIGURE CAPTIONS

### Figure 1: Proposed treatment algorithm for therapeutic plasma exchange (TPE) in paediatric neurology

Footnotes:

1. TPE has also been used in severe/fulminant presentations of stiff person syndrome, and in peripheral nervous system manifestations of systemic autoinflammatory diseases (see section Neurological indications for plasma exchange).
2. TPE has also been used in severe/fulminant presentations of Bickerstaff's brainstem encephalitis, Hashimoto's encephalopathy, opsoclonus-myoclonus syndrome, optic neuritis, PANS/PANDAS, paraneoplastic encephalitis, Rasmussen encephalitis, Sydenham's chorea, and in central nervous system manifestations of systemic autoinflammatory diseases (see section Neurological indications for plasma exchange).
3. TPE may be considered earlier in life-threatening situations.
4. See Nosadini et al. and Dale et al. for a broader overview of acute immunotherapeutic strategies (5, 6).
5. Mandatory for membrane filtration TPE; preferable for centrifugation TPE, especially in younger children.
6. If there is a history of previous transfusion reaction corticosteroids can also be used.
7. Oral sedation may also help younger children tolerate the procedure.

### Figure 2: Idealised kinetics of a plasma exchange course for removal of a typical IgG-class autoantibody

Footnotes: none

### Figure 3: Comparison of IVIG and TPE as first-line therapy in paediatric neurology

Footnotes: none

## **CONTRIBUTIONS**

ME, CH and ML conceived the project.

ME carried out the literature review and wrote the first draft of the manuscript.

YH, CB, CH and ML critically revised the manuscript and contributed to the final version.

## **DISCLOSURES**

ME, YH and CB have nothing to disclose.

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