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Review article

Therapeutic Plasma Exchange in the Neurologic Intensive Care Setting

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Abstract

Therapeutic plasma exchange (TPE) is a well-established therapeutic procedure commonly used in many neurological immune-mediated disorders. It is thought that the beneficial effects of TPE occur through elimination of pathognomonic autoantibodies, immune complexes, inflammatory mediators, complement components, and cytokines which play a crucial role in many kinds of neurological autoimmune disease. In various neurological disorders, randomized controlled studies have demonstrated the efficacy of TPE (eg, in acute inflammatory demyelinating polyneuropathy /AIDP; Guillain-Barre´ syndrome/, chronic inflammatory demyelinating polyradiculoneuropathy /CIDP/, myasthenia gravis /MG/, and paraproteinemic polyneuropathies /PP/). For these disorders TPE is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment. Although widely used, the potential benefit of TPE in the treatment of acute disseminated encephalomyelitis (ADEM), chronic focal encephalitis (Rasmussen's encephalitis), Lambert-Eaton myasthenic syndrome (LEMS), multiple sclerosis (MS), and neuromyelitis optica (NMO; Devic's disease) is less clear. For these disorders TPE is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.

Key words: intensive care setting, neuroimmunological disorders, therapeutic plasma exchange.

Introduction

There have been great developments in the fields of medical technology and new medication, but we still are facing diseases that have no good treatments available. It is known that autoantibodies and immune complexes play a crucial role in many kinds of autoimmune disease. Removing these pathogenic substances from the plasma of patients may be an efficient means of treatment. When therapeutic plasma exchange (TPE) became clinically available in the early 1970s, several spectacular treatment results in otherwise deleterious clinical situations were reported. These included life-threatening pulmonary hemorrhage in acute inflammatory demyelinating polyradiculoneuropathy (AIDP; Goodpasture's syndrome), myasthenic crisis, and thrombotic thrombocytopenic purpura (TTP) [1-3].

Data published during the last 30 years allow a more critical view on the role of TPE in the intensive care setting.

Therapeutic plasma exchange has become an established therapeutic procedure in neurological practice for numerous pathologic conditions. In fact, the latest review of plasma exchange use by the Canadian Apheresis Group indicates that 3 neurological disorders, myasthenia gravis (MG), Guillain-Barre syndrome, and chronic inflammatory demyelinating polyneuropathy (CIDP) are among the 5 most frequent indications for this therapy [4]. The neurological indications belong primarily to Category I or II, according to the guidelines of *the American Society for Apheresis* [5] (Table 1).

To define the current role of TPE, Brunetta-Gavranic B *et al.* retrospectively analyzed changes in indications for TPE in our database, that contains information on all TPEs conducted during 27 years at University Hospital Centre Zagreb (a national referral center for therapeutic apheresis, which covers approximately 90-95% of all TPEs performed in Croatia) [6]. The number of patients, (including children and elderly people) who underwent this procedure and TPEs increased several-folds over 27 years of follow-up despite changes in the pattern of indications and the emergence of new, more selective therapeutic options (LDL-apheresis, immunoadsorption, etc.). The disorder that most frequently resulted in an indication for TPE was myasthenia gravis (577 indications; 55% of all indications), with 2,783 procedures done over 27 years. The second most common indication for TPE was thrombotic thrombocytopenic microangiopathy (TTP and hemolytic uremic syndrome - HUS) with 91 indications and 1,060 TPE procedures. The third was Guillain-Barre syndrome (84 indications; 498 procedures). The number of TPEs performed for desensitization before bone marrow transplantation and for hyperviscosity syndrome due to Waldenström mac-

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roglobulinemia and multiple myeloma also increased significantly in the last decade (41 indications, 83 TPEs; 25 indications, 161 TPEs, respectively). It has been recorded a comparable increase in the number of patients who needed TPE for rapidly progressive glomerulonephritis (28 patients; 280 TPE) [5].
Most neurological disorders that are treated with TPE are associated with presumed aberrant humoral immune responses, including MG, Guillain-Barre syndrome, and CIDP [7]. The efficacy of TPE in these neurological desorders has been demonstrated in randomized controlled clinical trials, and the level of recommendation is high.
This article will review only those situations in which a rapid decision, whether to use TPE or not, in seriously ill neurologic patients is necessary.

Technical aspects of therapeutic plasma exchange

Therapeutic plasma exchange is an eytracorporeal blood purification technique, designed for the removal of large-molecular-weight substances from the plasma. A plasma filter is used to separate the plasma from all other cellular elements, using s semipermeable membrane. Plasma filter membrane pores are up to 0.2 µm in diameter (approximately 30 times the diameter of pores in conventional high-flux hemofilter membranes), allowing the removal of substances up to a molecular weight of 3 x 10^6 Da, which includes immunoglobulins, immune complexes, complement factors, lipoproteins, and endotoxin. As TPE removes all circulating substancesin the plasma, care should be taken to avoid disturbances with clotting factors, calcium and magnesium levels, and any other substances that may be depleted as a result of the procedure. Systemic heparinization is used for anticoagulation. The fluid volume removed by TPE must be replaced to prevent marked volume depletion. In most pathologic conditions in which plasma exchange is used, 1 to 1.5 plasma volumes (PV) are exchanged per procedure *per* day. There is no consensus on the ideal replacement solution for plasma discarded during TPE. Except for distinct diseases like TTP or hemolytic uremic syndrome (HUS) in which substitution is clearly by fresh-frozen plasma (FFP), colloid replacement can be achieved with the use of FFP, albumin, albumin and saline, or albumin and plasma expander solutions [8]. Routine treatment durations of 3 to 5 days may be prolonged, depending on the diagnosis and the individual patient's condition.
Complications associated with TPE might be related to blood access, replacement fluids, the procedure itself, or to the use of anticoagulants. Awareness of the possible severe complications is one of the major barriers for some physicians when considering TPE for their patients. Interestingly, although thousands of procedures are carried out each year, there are only a few reports on complications of TPE [9].

Table 1. Neurologic Indication Categories for Urgent Therapeutic Apheresis

Disease name	Category	Recommendation grade
Acute inflammatory Demyelinating polyneuropathy (Guillain-Barre´ Syndrome)	I	1A
Chronic inflammatory demyelinating polyradiculoneuropathy	I	1B
Myasthenia gravis	I	1A
Paraproteinemic polyneuropathies*	I	1B or 1C
Acute disseminated encephalomyelitis	II	2C
Chronic focal encephalitis (Rasmussen'sEncephalitis)	II	2C
Lambert-Eaton myasthenic syndrome	II	2C
Multiple sclerosis**	II	1B
Neuromyelitis optica (Devic's Syndrome)	II	1C

*Special condition: IgA/IgG – recommendation grade, 1B; IgM – recommendation grade, 1C
**Special condition: Acute CNS inflammatory demyelinating disease unresponsive to steroids

Medical and scientific basis for therapeutic use of plasma exchange

There are several mechanisms by which TPE exerts its beneficial effects. The removal of circulating autoantibodies, immune complexes, cytokines, and other inflammatory mediators is thought to be the principal mechanism of action. Antibodies against self have been identified in various neurological disorders, including antibodies against nicotinic acetylcholine receptor in MG, antibodies against P/Q-type voltage-gated calcium channels in Lambert-Eaton syndrome, and antimyelin oligodendrocyte glycoprotein antibodies in MS. Cytokines, including chemokines and

complement, are other potentially injurious molecules that may be removed by plasmapheresis. Several othereffects of TPE on immune function have been proposed, including immunomodulatory actions such as alterations in idiotypic/anti-idiotypic antibody balance, a shift in the antibody-to-antigen ratio to more solubile formsof immune complexes, and stimulation of lymphocyte clones to enhance cytotoxic therapy [10]. The infusion of normal plasma may also replace a deficient plasma component, perhaps the principal mechanism of action of TPE in TTP.

Clinical benefit from TPE is primarily observed in diseases with a self-limited course, whereas a long-term effect in chronic disorders is less frequently achieved. In antibody-mediated diseases, this could be due to the removal of an insufficient number of pathogenic autoantibodies and their continued synthesis with repeated antigenic stimulation. The intravascular and extravascular distribution of pathogens that are desired to be removed by TPE has to be considered. Most large molecular weight substances have considerable concentrations in the extravascular space, and after removal of the substance from intravascular space, there may be a rapid substance redistribution from extravascular into the intravascular space. It usually requires repeated treatments with TPE. Complete removal of pathogenic antibodies is impossible to achieve. Because of a slow equilibration of large macromolecules between the vascular space and the interstitium, the rate of removal can be expressed as a first-order kinetic. The exchange of a single volume of plasma will lower the level of a specific macromolecule by 50% to 60%, and an increase to 1.4 PV will lower plasma levels by 75% [11].

Therapeutic plasma exchange in neuroimmunological disorders

Acute inflammatory demyelinating polyradiculoneuropathy (AIDP; Guillain-Barré syndrome)

Acute inflammatory demyelinating polyradiculoneuropathy (AIDP; Guillain-Barré syndrome) has emerged in the past quarter century as the most frequently occurring clinical paralytic disorder. Annual incidence approaches 2 cases *per* 100,000 persons, up to 23% may require assisted ventilation, and up to 1 in 20 patients may die from complications of the disease. About 75% of patients suffer persistent minor neurological deficits, 5% to 15% are disabled by the residua of their disease and up to 10% relapse. Mortality is estimated at 5%. Guillain-Barré syndrome is characterized by generalized weakness and distal paresthesias progressing over several days. A typical diagnostic feature is an increased concentration of protein in the absence of a pleocytosis (albumino-cytologic dissociation) in the cerebrospinal fluid. The typical case of Guillain-Barré syndrome presents initially with paresthesias of the toes or fingertips, but within days, leg weakness sufficient to interfere with walking or stair climbing develops. Weakness of the arm, facial, and oropharyngeal muscles ensues as the paresthesias extend proximally. Symmetric limb weakness and absent deep tendon reflexes are common findings. Sensory loss is relatively mild despite the paresthesias. Autonomic dysfunction may case variability in heart rate and blood pressure. Spontaneous recovery may occur usualy after three weeks of illness [12]. Clinical variants include The Miller-Fisher variant is characterized by opthalmoplegia, ataxia, and areflexia without weakness.

Aberrant humoral and cellular immune response systems are involved in the pathogenesis of Guillain-Barre syndrome. Molecular mimicry, in which epitopes incidentally shared by microbial antigens and nerve structures elicit an autoreactive T-cell or B-cell response in the wake of an infective illness, may trigger the autoimmune process. In about 60% of cases, Guillain-Barre syndrome follows closely an infection, most frequently caused by the microbiological agent *Campylobacter jejuni*. Activated T cells migrate across the blood-nerve barrier and are reactivated in situ when their autoantigen is appropriately displayed by macrophages along with major histocompatibility complex II products and co-stimulatory molecules. Autoantibodies crossing the blood-nerve barrier en passant with T cells or accessing target structures directly at the most proximal or distal parts of the nerve contribute to the inflammatory process by antibody-dependent cytotoxicity and activation of complement. A large variety of antibodies against different glycolipids, including GM1, GD1a, and GQ1b, among others, have been described [12,13].

Severely affected patients with Guillain-Barre syndrome may require intensive care, mechanical ventilation, and assistance through the paralysis and necessary rehabilitation over several months to a year or more. Corticosteroids have not been shown helpful when used alone. TPE was the first therapeutic modality to impact the disease favorably and several major randomized controlled clinical trials have confirmed its efficacy (Table 2). In the first study, 245 patients were included and received TPE or conventional supportive therapy [14]. Clinical outcomes, that is, time to improve 1 clinical grade and time to independent walking, were assessed at 4 weeks and 6 months. In the study of the French Cooperative Group on Plasma Exchange in Guillain-Barre Syndrome [15], 220 patients were included, 109 of whom underwent TPE and were compared with 111 patients defined as the control group. Substantial benefit was documented for the primary end point, that is, time to recover the ability to ambulate with assistance, and in secondary factors such as the reduction of the proportion of patients who needed assisted mechanical ventilation, a more rapid time of onset of motor recovery, and clinical factors such as time to walk with and without assistance [15]. The same group reported also the long-term benefit in the TPE population as recovery of full muscle strength after 1 year in 71% of patients compared with 52% of subjects in the control group [16]. In 1997, an randomized, controlled, nonblinded trial, included and randomized to 3 groups according to degree of disability, 556 patients with Guillain-Barre syndrome. Patients with mild disability underwent either 0 or 2 TPE sessions, those with moderate disability underwent 2 or 4 sessions, and those with severe disability underwent 4 or 6 sessions. It could be demonstrated that 2 vs 0 TPE sessions in patients with mild disability and 4 vs 2 TPE sessions in patients with modera-

te disability were more beneficial. More than 4 treatments did not yield additional benefit in patients receiving mechanical ventilation in the group with severe disability [17]. Based on several studies of class I evidence, TPE has been established as effective treatment in the therapy of Guillain-Barre syndrome (Table 3). Plasma exchange is most beneficial when started within 7 days of disease onset, but is also efficacious when started after 30 days [18,19].

Chronic inflammatory demylinating polyradiculoneuropathy (CIDP)

Patients with CIDP have a progressive clinical course with worsening symmetric proximal and distal weakness. The progressive clinical symptoms last for longer than 8 weeks. This disorder may be seen in the setting of other underlyng diseases, including Hodgkin's disese, connective tissue diseases, inflammatory bowel disease, hepatitis, diabetes and infection with human immunodeficiency virus (HIV). Patients with monoclonal gammapathies can present similar findings. The diagnosis of CODP is largely clinicaly, but cerebrospinal fluid may reveal elevated protein. The nerve biopsies show histologic evidence of demyelination with mononuclear infiltrate. Evidence of demyelination is also present on electrophysiological testing [12,13]. The presence of autoantibodies against various proteins and glycolipids of the peripheral nerve in samples of serum and cerebrospinal fluid from patients with CIDP may provide a rationale for the therapeutic use of TPE (Table 4). Treatment usually consists of either corticosteroid therapy or intravenous immunoglobulin (IVIG) or TPE, followed by long-term immunosuppression with cyclosporine, interferon, azathioprine, cyclophosphamide, or other immunosuppressive therapies [5]. Therapeutic response is measured by improvement or stabilization in neurological symptoms, at which point treatment can be tapered or discontinued. Between 60% and 80% of patients respond to initial therapy but long-term prognosis varies [20].

Table 2. Trials for Therapeutic Plasma Exchange in Guillain-Barre´ Syndrome

Trials	Study characteristics and design	No. of patients	Outcome
Guillain-Barre Syndrome Study Group (14)	TPE vs supportive care. Single blinded	245	Improvement at 4 wk, time to improve 1 clinical grade, time to independent walking, outcome at 6 mo. in the TPE group.
French Cooperative Group on Plasma Exchange in Guillain-Barre´ Syndrome (15)	TPE (4x) with albumin vs TPE (4x) with FFP vs no TPE. Nonblinded	22	Shorter time to recover walking with assistance (30 vs 44 d; $P<0.01$) in TPE group; fewer patients requiring assisted ventilation, shorter time to onset of motor recovery. No differences between TPE groups.
French Cooperative Group on Plasma Exchange in Guillain-Barre´ Syndrome (17)	Three groups: mild disability, 0 vs 2 TPE; moderate disability, 2 vs 4 TPE; severe disability, 4 vs 6 TPE. Nonblinded	556	Two TPE more effective than 0 for time to onset of motor recovery (4 vs 8 d; $P<0.001$) in group with mild disability. Four TPE superior to 2 TPE for time to walk with assistance (20 vs 24 d; $P = 0.04$) in group with moderate disability. No difference between 4 and 6 TPE in group with severe disability.
Dutch Guillain-Barre´ Study Group (18)	TPE (5x) vs IVIG (0.4 g/kg per day, 5 d). Nonblinded, bias controlled.	150	Improvement 1 point on functional score, 34% in TPE group vs 53% in IVIG group ($P = 0.02$); time to improvement by 1 grade 41 vs 27 d ($P = 0.05$). Both treatments are of equal efficacy, but IVIG may be superior.
Plasma Exchange/ Sandoglobulin Guillain-Barre´ Syndrome Trial Group (19)	TPE (5x) vs IVIG (0.4 g/kg/d, 5 d) vs TPE (5x) + IVIG (0.4 g/kg/d, 5 d). Single blinded.	383	No significant difference in major outcome measure (improvement on disability scale after 4 wk) or secondary outcome measures (time to recovery of unaided walking and time to discontinuation of mechanical ventilation).

Table 3. Acute Inflammatory Demyelinating Polyneuropathy (AIDP; Guillain-Barre´ Syndrome)

Incidence	1 to 2 *per* 100,000/year
Category	I
Recommendation	Grade 1A
Type of evidence	Type I
Procedure	TPE
Replacement fluid	Albumin
Volume treated	1 to 1.5 PV
Frequency	Every other day

Duration/discontinuation/number of rocedures:
5 to 6 TPE over 10 to14 days are recommended.

Technical notes:
The typical TPE strategy is to exchange 200-250 mL of patient plasma *per* kg body weight over 10 to 14 days. This will generally require 5 to 6 TPE procedures with 5% albumin replacement. Fresh frozen plasma is not routinely used for replacement. Since autonomic dysfunction may be present, affected patients may be more susceptible to volume shifts, blood pressure and heart rate changes during extracorporeal treatment. Relapses may occur in approximately 10% of patients 2 to 3 weeks following either treatment with TPE. When relapses occur, additional therapy, usually TPE, can be helpful. In AIDP patients with axonal involvement, TPE has been reported to be of greater potential benefit than IVIG.

Myasthenia gravis (MG)

Myasthenia gravis (MG) is an autoimmune syndrome ca-

Table 4. Chronic Inflammatory Demylinating Polyradiculoneuropathy (CIDP)

Incidence	1 to 2 *per* 100,000/year
Category	I
Recommendation	Grade 1B
Type of evidence	Type I
Procedure	TPE
Replacement fluid	Albumin
Volume treated	1 to 1.5 PV
Frequency	2 to 3 PE/week until improvement, then taper as tolerated

Duration/discontinuation/number of rocedures:
TPE provides short-term benefit but rapid deterioration may occur afterwards. This may necessitate maintenance treatment, with TPE and/or other immunomodulating therapies, which should be tailored to the individual patient. The frequency of maintenance TPE may range from weekly to monthly as needed to control symptoms.

used by the failure of neuromuscular transmission (clinically characterized by fluctuating muscle weakness and fatigability), which results from the binding of autoantibodies to proteins involved in signaling at the neuromuscular junction. The most common variant of the disease is mediated by circulating autoantibodies against the nicotinic acetylcholine receptor (AChR). These antibodies can be detected in 75% to 95% of patients with MG. Mechanisms responsible for loss of functional AChR that compromise or abort safe neuromuscular transmission include the degradation of the AChR, complement-mediated lysis of the AChR, and interference with neurotransmitter binding. In subgroups of patients negative for AChR antibody, other antibodies with different specificities can be detected, for example, antibodies against the muscle-specific receptor tyrosine kinase [21].

The disease is characterized by weakness and fatigability with repetitive physical activity, which usually improves with rest. Common presentation includes ptosis and diplopia with more severe cases having facial, bulbar, and limb muscle involvement. The disease is more prevalent in 20-40 year old women.

Myasthenic crisis is characterized by acute respiratory failure requiring intubation, prolonged intubation following thymectomy, or bulbar weakness causing dysphasia and high risk of aspiration. Thymic abnormalities, such as hyperplasia or thymoma, are commonly associated with MG. Otherwise, crisis may be precipited by other illnesses, such influenza or other infections.

With modern treatment regimens the mortality from MG has greatly decreased from 30% to less than 5%. The four major treatment approaches include cholinesterase inhibitors, thymectomy, immunosuppression, and either TPE or IVG. Cholinesterase inhibitors (e.g. pyridostigmine bromide) delay the breakdown, and increase the availability, of acetylcholine at the motor end plate and lead to variable improvement in strength. Thymectomy leads to clinical improvement in many patients under the age of 65, but it may take years for the benefits to show. Immunosuppressive drugs (corticosteroids, cyclosporine, azathioprine, and tacrolimus) have a delayed effect and therefore play an important role in long-term rather than short-term management. Plasma exchange might be useful in myasthenic crisis and in the preoperative and postoperative phases of thymectomy in severe forms of myasthe-

Table 6. Paraproteinemic Polyneuropathies (PP)

Incidence	Monoclonal gammapathy of undetermined significance: up to 3% of general population over 50 years old
Category	
- **demyelinating polyneuropathy with IgG/IgA**	I
- **polyneuropathy with IgM**	I
Recommendation	
- **demyelinating polyneuropathy with IgG/IgA**	Grade 1B
- **polyneuropathy with IgM**	Grade 1C
Type of evidence	Type I
Procedure	TPE
Replacement fluid	Albumin; plasma
Volume treated	1 to 1.5 PV
Frequency	Every other day

Duration/discontinuation/number of rocedures:
The typical course is 5 to 6 treatments over the course of 10 to 14 days. Long term TPE or slow tapering off TPE can be considered. The patient may continue to improve over weeks following cessation of TPE. If the level of paraprotein is correlative to the polyneuropathy then it can be monitored to evaluate the frequency of treatment. However, the titer of the paraprotein may not correlate with the clinical disease state.

Technical notes:
Patients with demyelinating PP may be treated at any time in their course (including patients referred up to 4 years after onset of symptoms).

nia gravis [22,23]. It is presumed that elimination of circulating AChR antibodies and other humoral factors of pathological significance account for the observed beneficial effects of TPE. Both seropositive and seronegative patients respond to TPE. Clinical effect can be apparent within 241 antigens, by transfer of serum from patients with the disease, and by intraneural injection. In all these instances the case for pathogenic activity of IgM antibodies directed against myelin glycoprotein (MAG), gangliosides, and other glycosphingolipids is better established than that for other antigens and for IgG and IgA antibodies.

In a randomized, controlled, double-blind trial, Dyck *et al.* [28] studied the effectiveness of TPE in the treatment of polyneuropathy associated with MGUS. Thirty-nine patients were randomly assigned to receive either TPE twice weekly for 3 weeks or sham treatment. Based on its effects on the 2 primary outcome measures, that is, the neuropathy disability score and the summed compound-muscle action potentials of motor nerves, a treatment benefit was suggested for TPE, whereas in secondary end points,that is, nerve conduction velocity and sensory nerve action potentials, no statistically significant differences were found. The study demonstrated, furthermore, that patients with IgG or IgA gammopathy benefit more than those with IgM gammopathy. Hence, TPE can be recommended in at least this subgroup of patients (Table 6).

Acute Disseminated Encephalomyelitis (ADEM)

Acute disseminated encephalomyelitis (ADEM) is a neurological disorder characterized by inflammation of the brain and spinal cord caused by damage to the myelin sheath. The myelin sheath is the fatty covering, which acts as an insulator, on nerve fibers in the brain. ADEM may occur in association with a viral or bacterial infection, as a complication of inoculation or vaccination, or without a preceding cause. Onset of the disorder is sudden. Symptoms, which vary among individuals, may include headache, delirium, lethargy, coma, seizures, stiff neck, fever, ataxia, optic neuritis, transverse myelitis, vomiting, and weight loss. Other symptoms may include monoparesis (paralysis of a single limb) or hemiplegia (paralysis on one side of the body). The disorder occurs in children more often than in adults. The mortality rate is around 5%, with complete recovery in 50% to 75% of cases [29].

MRI is the diagnostic imaging modality of choice for the demyelinating lesions of ADEM. Characteristic lesions seen on MRI appear as patchy areas of increased signal intensity with typical involvement of deep cerebral hemispheric and subcortical white matter, as well as lesions in the basal ganglia, gray-white junction, brain stem, cerebellum and spinal cord.

The therapeutic aim is to abbreviate the central nervous system (CNS) inflammatory reaction as quickly as possible, and to speed up clinical recovery. Corticosteroids are considered effective because of their anti-inflammatory and immunomodulatory effects with additional beneficial effect on cerebral edema. Corticosteroids hasten recovery and result in clinical improvement in up to 60% of patients. TPE should be considered for patients with severe ADEM, who respond poorly to steroid treatment or in whom it is contraindicated. TPE is used and has a clearly defined role in other neurological conditions that are presumed to be immunologically mediated. TPE works by removing presumed offending autoantibodies as well as through immunomodulation (Table 7). In the acute phase of ADEM, cytokines such as tumor necrosis factor, soluble tumor necrosis factor receptor 1, IL-6 and IL-10 are elevated. Antibodies to gangliosides, such as GM1 and CD1a, and myelin basic protein-reactive T-helper 2 cells, may be present, which can be removed by TPE [5].

Table 7. Acute Disseminated Encephalomyelitis (ADEM)

Incidence	0.8 *per* 100,000/year
Category	II
Recommendation	Grade 2C
Type of evidence	Type III
Procedure	TPE
Replacement fluid	Albumin
Volume treated	1 to 1.5 PV
Frequency	Daily or every other day

Duration/discontinuation/number of rocedures:
There is no clear standard based upon which to make recommendations as to the optimum use of TPE in ADEM. In the largest case study, TPE achieved moderate and marked sustained improvement in 50% of the patients. Factors associated with improvement include male sex, preserved reflexes and early initiation of treatment. In most published literature, response was noticeable within days, usually after 2 to 3 exchanges. If improvement is not observed early in treatment, then it is unlikely a response will occur. TPE therapy consists of 3 to 6 treatments.

Chronic Focal Encephalitis (Rasmussen's Encephalitis)

Rasmussen's encephalitis, a form of chronic focal encephalitis, is a rare inflammatory brain disease characterized by severe intractable epilepsy, and unilateral progressive motor defect associated with controlateral hemispheric atrophy. The disorder usually affects children, although occasional reports of adult-onset Rasmussen's syndrome have been reported. Cumulative evidence suggests that Rasmussen encephalitis has an autoimmune etiology. Pathologic hallmarks are inflammation and gliosis in the affected cerebral hemisphere. Focal disruption of the blood-brain barrier, perhaps caused by focal seizures, may allow the access of pathologic humoral factors to brain tissue. Antibodies have been detected in serum samples of patients with Rasmussen encephalitis that are directed against the glutamate receptor GluR3. A major pathogenic role of anti-GluR3 antibodies has been challenged because they have also been identified in patients with focal epilepsy and (in lower frequency) in other neurological diseases, and their contribution remains unresolved. Cytotoxic CD8 T cells have been identified in the brains of affected individuals with Rasmussen encephalitis, and it has been suggested that their direct assault on neurons underlies disease pathogenesis [10].

Clinical diagnosis in the early stages is often difficult as the patient may present with generalized seizures, but the later stage is easier to recognize when the patients presents with epilepsia partialis and hemiparesis. A combination

of clinical criterion, imaging studies, electroencephalography and antibody titres will identify most cases.
Anticonvulsives are necessary, but not always effective. Based on recent pathogenic concepts, different medical treatments including IVIG, iv. methylprednisolone and oral prednisone, intraventricular interferon-a given via Omaya reservoir, iv. rituximab and tacrolimus have been investtigated for control of epileptic and neurological aspects of Rasmussen's syndrome. Surgical hemispheric disconnection that appears the most effective treatment in children to improve seizure control is not indicated in adults for evident functional reasons. Significant early improvement has been shown in children with Rasmunssen encephalitis with TPE. This treatment was based on the demonstration on serum immunoreactivity to the GluR3 in such patients [5,30]. Despite the paucity of clinical reports, investigators in the field recommend a concerted trial of immunotherapy, including TPE (Table 8), to control seizures, mitigate functional decline, and delay the need for hemispherectomy in patients with Rasmussen's encephalitis.

Table 8. Chronic Focal Encephalitis (Rasmussen's Encephalitis)

Incidence	Rare
Category	II
Recommendation	Grade 2C
Type of evidence	Type II-3
Procedure	TPE
Replacement fluid	Albumin/saline
Volume treated	1.5 to 2 PV
Frequency	TPE: 3-6 TPE over 6-12 days; repeat monthly Alternative schedule: TPE weekly

Duration/discontinuation/number of rocedures:
After an initial course of treatment, subsequent courses of TPE (with or without IVIG) may be performed at intervals of 1 to 2 weeks or up to 2 to 3 months as empirically needed to maintain clinical stability and avoid or delay hemispherectomy. Immunosuppressive medications may increase the interval between courses. Surgical treatment is offered for the management of patients who exhibit functional or cognitive decline or intractable seizure activity despite intensive immunomodulatory therapy.
Technical notes:
Neuropsychological assessment may be helpful in evaluating patients with slowly progressive disease to determine whether TPE is effective in postponing surgical therapy.

Lambert-Eaton Myasthenic Syndrome (LEMS)

Lambert-Eaton myasthenic syndrome (LEMS) is an immune-mediated, presynaptic neuromuscular junction disorder mediated by antibodies against neuronal P/Q-type voltage-gated calcium channels. The disease is characterized by muscle weakness and autonomic dysfunction. In more than 90% of the patients the muscle weakness starts proximally in the legs, and thereafter may spread to other skeletal muscles in a caudo-cranial order. In some patients this might lead to a need for artificial respiration. Ptosis and diplopia can be present, but tend to be milder than in autoimmune myasthenia gravis. Mild to moderate autonomic dysfunction in LEMS is characterized by the presence of a dry mouth, dryness of the eyes, blurred vision, impotence and obstipation, and is mostly mild to moderate. In about 60% of patients, LEMS is associated with small cell lung carcinoma, but it can also occur outside the context of neoplasia. In rare cases patients with LEMS and a small cell lung cancer develop a paraneoplastic cerebellar degeneration [31].
Initial management should be directed at treatment of the underlying malignancy because weakness frequently improves with effective cancer therapy. Apart from underlying malignancy, management of LEMS is directed toward support immunosuppression to control production of the offending antibodies and support of acetylcholine-mediated neurotransmission to improve neurological function. Cholinesterase inhibitors such as pyridostigmine alone, or combined with guanidine hydrochloride, that act to enhance release of acetylcholine from the presynaptic nerve terminal, may produce some improvement in LEMS. 3,4-diaminopyridine is effective therapy in LEMS and may be combined with pyridostigmine [5,24]. In patients with significant weakness, prednisone, azathioprine, cyclosporine or cyclophosphamide can be used. The identification of LEMS as an autoantibody-mediated syndrome has led to several attempts to use TPE and IVIG in its treatment (Table 9). TPE may be a useful adjunct to management of patients with LEMS whose neurological deficit is severe or rapidly developing, or patients who are too uncomfortable to wait for immunosuppressive or aminopyridine drugs to take effect, or who cannot tolerate treatment with IVIG.The effects are shortlived unless immunosuppressant drugs are used, and additional courses are often needed to maintain benefit. Improvment may last for longer and longer periods after each treatment.

Table 9. Lambert-Eaton Myasthenic Syndrome (LEMS)

Incidence	Rare
Category	II
Recommendation	Grade 2C
Type of evidence	Type II-3
Procedure	TPE
Replacement fluid	Albumin
Volume treated	1 to 1.5 PV
Frequency	Daily or every other day

Duration/discontinuation/number of rocedures:
Treatment should continue until a clear clinical and EMG response is obtained or at least until a 2 to 3-week course of TPE has been completed. Repeated courses may be applied in case of neurological relapse, but the effect can be expected to last only 2 to 4 weeks in the absence of immunosuppressive drug therapy.
Technical notes:
The reported TPE regimens vary from 5-15 daily TPE over 5-19 days to 8-10 TPE carried out at 5-7 day intervals. Most reports indicate an exchange volume of 1.25 plasma volumes. **Of note**: improvement may not be seen for the 2 weeks or more after initiation of plasma exchange therapy. This may be due to the slower turnover of the presynaptic voltage gated calcium channel compared to the postsynaptic acetylcholine receptor.

Multiple Sclerosis (MS)

Multiple sclerosis is a multifocal inflammatory disease of the CNS, characterized by chronic inflammation, demyelination, axonal damage, and subsequent gliosis. Current concepts of its pathogenesis assume that in genetically susceptible individuals potentially self-reactive T cells are activated in the immune system, home onto the CNS, and may initiate tissue damage *via* release of inflammatory cytokines, stimulation of B cells and macrophages, and activation of the complement system. Antibodies against myelin basic protein and myelin oligodendrocyte glycolprotein have been detected in subgroups of patients with MS. These antibodies may mediate injury by complement fixation or linking with innate immune effector cells such as macrophages [32].

Clinical symptoms include sensory disturbances, unilateral optic neuritis, diplopia, limb weakness, gait ataxia, neurogenic bladder and bowel symptoms. MRI shows multiple lesions of different ages involving the white matter of the cerebrum, brain stem, cerebellum, and spinal cord. A more severe clinical course can be predicted by frequent relapses in the first 2 years, primary progressive form, male sex, and early permanent symptoms [10].

Patients with MS may have benefit from TPE by removing an autoantibody, such as anti-myelin antibody, or modulating immune response. In acute, severe attacks of MS in patients who fail initial treatment with high-dose steroids, TPE may be beneficial (Table 10). However, no major therapeutic effect of TPE can be expected once antibodies are deposited in situ in CNS lesions. Treatment in relapsing-remitting MS includes: azathioprine, IVIG, interferon b-1a, glatiramer acetate, mitoxantrone hydrochloride, natalizumab, and cyclophosphamide depending on the disease severity. TPE has not been specifically studied in relapsing-remitting MS. An adequate treatment for primary progressive MS does not exist. Multiple randomized controlled trials demonstrate small to no benefit of TPE in conjunction with other immunosuppressive drugs in patients with chronic progressive MS [5,33].

Table 10. Multiple Sclerosis (MS)

Incidence	5 to 30 *per* 100,000/year
Category	
- **acute CNS inflammatory demyelinating disease unresponsive to steroids**	II
Recommendation	Grade 1B
Type of evidence	Type I
Procedure	TPE
Replacement fluid	Albumin
Volume treated	1 to 1.5 PV
Frequency	Acute 5 to 7 (or even 14 days)

Duration/discontinuation/number of rocedures:
In acute MS unresponsive to steroids, 5 to 7 TPE procedures have a response rate of approximately 50%.

Neuromyelitis Optica (NMO; Devic's Disease)

Neuromyelitis optica (NMO; Devic's syndrome) is a severe idiopathic inflammatory demyelinating disease that selectively affects optic nerves and spinal cord, typically spares the brain, and generally follows a relapsing course. Over 70% of cases of NMO are associated with NMO-IgG which binds to aquaporin-4 (a water channel) on astrocyte foot processes at the blood brain barrier. Histopathology of NMO includes deposition of IgG and complement in the perivascular space with a granulocyte and eosinophil infiltrate, and hyalinization of vascular walls [5,34]. Within 5 years, 50% of patients lose functional vision in at least one eye or are unable to walk independently. Early and accurate diagnosis is important because NMO carries a poorer prognosis than MS and generally accepted treatment approaches differ [34]. Distinction from MS is by female predominance (1:4-5 male: female), longitudinal spinal cord lesions (3 or more vertebral segments), and cerebrospinal fluid (CSF) with negative oligoclonal IgG bands and with leukocytosis [35]. In addition brain MRI is not typical for MS. NMO is associated with other autoimmune diseases, such as systemic lupus erythematosus (SLE), Sjogren's, MG, viral infections and vaccinations. Disease course may be a monophasic or relapsing. Monophasic course is associated with younger age at disease onset and equal male:female predominance. Monophasic course has a 90% 5 year survival rate. Approximately 80% of patients with NMO have relapsing coarse, which has a poor prognosis: 50% of patients become legally blind or wheelchair bound and 30% die respiratory failure within 5 years [5]. NMO worsens by incomplete recovery with each acute attack.

Acute attacks are managed by high-dose intravenous steroids and, if failure to resolve symptoms TPE is added. TPE removes the pathologic antibody, immune complexes, and inflammatory mediators. Relapses are commonly resistant to steroids, and TPE can be helpful in recovery from acute attack but does not prevent further relapses (Table 11). Prophylaxis to prevent further acute attacks includes immunosuppressive medications and immunomodulation, such as rituximab (anti-CD20), methotrexate, interferon, azathioprine, cyclophosphamide, prednisone, IVIG, mitoxantrone, interferon, and mycophenolate mofetil [36]. Patients at high risk for relapse include those who are seropostive for NMO-IgG.

Table 11. Neuromyelitis Optica (NMO; Devic's Disease)

Incidence	Rare
Category	II
Recommendation	Grade 1C
Type of evidence	Type II-3
Procedure	TPE
Replacement fluid	Albumin
Volume treated	1 to 1.5 PV
Frequency	Daily or every other day

Duration/discontinuation/number of rocedures:
The majority of studies performed 5 TPE on average (range 2 to 20 procedures). The patients who received TPE had lower residual disability scores (the results from the retrospective cohort study). In case series 50% to 70% of patients showed improvement after TPE, but all patients had received steroids.

Conclusions

The role of TPE in the neurologic intensive care unit has chenged over past 35 years. It is known that autoantibodies and immune complexes play a crucial role in many kinds of neurological autoimmune disease. It has been recognized that removing these (autoantibodies and immune complexes) and some other pathogenic substances (inflammatory mediators, complement components, and cytokines) from the plasma of patients is an efficient means of treatment. In various neurological disorders, randomized controlled studies have demonstrated the efficacy of TPE (eg, in acute inflammatory demyelinating polyneuropathy /AIDP; Guillain-Barre´ Syndrome/, chronic inflammatory demyelinating polyradiculoneuropathy /CIDP/, myasthenia gravis /MG/, and paraproteinemic polyneuropathies/ PP/). For these disorders TPE is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment. Although widely used, the potential benefit of TPE in the treatment of acute disseminated encephalomyelitis (ADEM), chronic focal encephalitis (Rasmussen's encephalitis), Lambert-Eaton myasthenic syndrome (LEMS), multiple sclerosis (MS), and neuromyelitis optica (NMO; Devic's disease) is less clear. For these disorders TPE is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.

Conflict of interest statement. None declared.

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