Acta Clin Croat 2012; 51:137-153 Review

THERAPEUTIC PLASMA EXCHANGE IN THE NEUROLOGIC INTENSIVE CARE SETTING RECOMMENDATION FOR CLINICAL PRACTICE

Petar Kes[1], Vanja Bašić-Kes[2], Nikolina Bašić-Jukić[1] and Vida Demarin[2]

[1]Department of Nephrology, Arterial Hypertension and Dialysis, University Department of Internal Medicine, Zagreb University Hospital Center; [2]University Department of Neurology, Sestre milosrdnice University Hospital Center, Zagreb, Croatia

SUMMARY – Therapeutic plasma exchange (TPE) is a well-established therapeutic procedure commonly used in many neurologic 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 neurologic autoimmune disease. In various neurologic disorders, randomized controlled studies have demonstrated the efficacy of TPE (e.g., in acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome), chronic inflammatory demyelinating polyradiculoneuropathy, myasthenia gravis and paraproteinemic polyneuropathies). 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, chronic focal encephalitis (Rasmussen's encephalitis), Lambert-Eaton myasthenic syndrome, multiple sclerosis and neuromyelitis optica (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: *Acute disseminated encephalomyelitis; Acute inflammatory demyelinating polyneuropathy; Chronic focal encephalitis; Chronic inflammatory demyelinating polyradiculoneuropathy; Lambert-Eaton myasthenic syndrome; Multiple sclerosis; Myasthenia gravis; Neuromyelitis optica; Paraproteinemic polyneuropathies; Therapeutic plasma exchange*

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 patient plasma 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 for a more critical view on the role of TPE in the intensive care setting.

Therapeutic plasma exchange has become an established therapeutic procedure in neurologic practice

Correspondence to: *Prof. Petar Kes, MD, PhD*, Department of Nephrology, Arterial Hypertension and Dialysis, University Department of Internal Medicine, Zagreb University Hospital Center, Kišpatićeva 12, HR-10000 Zagreb, Croatia
E-mail: kespetar@net.hr

Received November 14, 2011, accepted January 10, 2012

Table 1. Neurologic indication categories for urgent therapeutic apheresis (TA)

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

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

for numerous pathologic conditions. In fact, the latest review of plasma exchange use by the Canadian Apheresis Group indicates that 3 neurologic disorders, myasthenia gravis (MG), Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy (CIDP) are among the 5 most frequent indications for this therapy[4]. The neurologic 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-Gavranić *et al.* retrospectively analyzed changes in the indications for TPE in our database, which contains information on all TPEs conducted during 27 years at Zagreb University Hospital Center (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-fold over 27 years of follow-up despite changes in the pattern of indications and the emergence of new, more selective therapeutic options (LDL-apheresis, immunoadsorp-

Table 2. Indications for therapeutic apheresis[5]

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

tion, etc.). The disorder that most frequently resulted in an indication for TPE was myasthenia gravis (MG; 577 indications, 55% of all indications), with 2783 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 1060 TPE procedures. The third was Guillain-Barré syndrome (84 indications, 498 procedures). The number of TPEs performed for desensitization before bone marrow transplantation and for hyperviscosity syndrome due to Waldenström macroglobulinemia and multiple myeloma also increased significantly in the last decade (41 indications, 83 TPEs and 25 indications, 161 TPEs, respectively). A comparable increase has been recorded in the number of patients who needed TPE for rapidly progressive glomerulonephritis (28 patients; 280 TPEs)[5].

Most neurologic disorders that are treated with TPE are associated with presumed aberrant humoral immune responses, including MG, Guillain-Barré syndrome, and CIDP[7]. The efficacy of TPE in these neurologic disorders has been demonstrated in randomized controlled clinical trials, and the level of recommendation is high (Tables 2 and 3).

Table 3. Grading recommendations

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

RCT = randomized controlled trial

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 extracorporeal blood purification technique, designed for the removal of large-molecular-weight substances from the plasma. A plasma filter is used to separate plasma from all other cellular elements using a semipermeable membrane. Plasma filter membrane pores are up to 0.2 μm in diameter (approximately 30 times the diameter of the pores in conventional high-flux hemofilter membranes), allowing for the removal of substances of a molecular weight up to $3x10^6$ Da, which includes immunoglobulins, immune complexes, complement factors, lipoproteins, and endotoxin. As TPE removes all circulating substances in 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 done 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 duration 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].

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 neurologic 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 multiple sclerosis (MS). Cytokines, including chemokines and complement, are other potentially injurious molecules that may be removed by plasmapheresis. Several other effects 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 soluble forms of 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 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 slow equilibration of large macromolecules between the vascular space and the interstitium, the rate of removal can be expressed as first-order kinetics. 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 Neuroimmune 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 neurologic 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 pleocytosis (albumino-cytologic dissociation) in the cerebrospinal fluid (CSF). A 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 cause variability in heart rate and blood pressure. Spontaneous recovery may occur usually after three weeks of illness[12]. Clinical variants include the Miller-Fisher variant characterized by ophthalmoplegia, ataxia, and areflexia without weakness.

Aberrant humoral and cellular immune response systems are involved in the pathogenesis of Guillain-Barré 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-Barré 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[7,12].

Severely affected patients with Guillain-Barré syndrome may require intensive care, mechanical ventilation (Fig. 1), 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 4). In the first study, 245 patients were included and received TPE or conven-

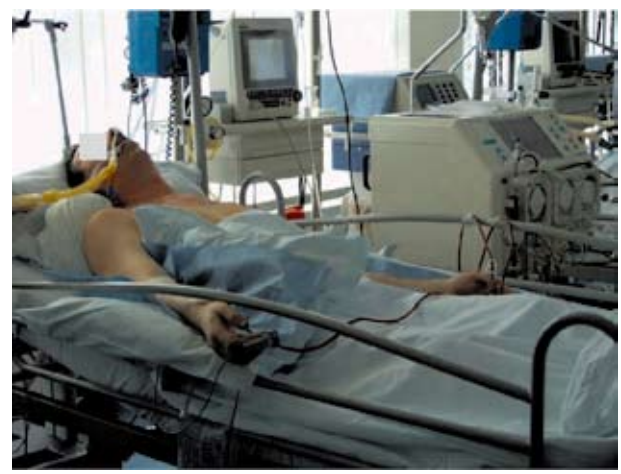

Fig. 1. Patient with acute inflammatory demyelinating polyneuropathy (AIDP; Guillain-Barré syndrome) on mechanical ventilation at Neurologic Intensive Care Unit, Zagreb University Hospital Center, Zagreb, Croatia. Guillain-Barré syndrome is the most common cause of rapidly progressive weakness due to peripheral nerve involvement that evolves rapidly (usually over days) and classically has been described as ascending from legs to arms and, in severe cases, to respiratory and bulbar muscles. Between 10% and 25% of patients require ventilator assistance initiated within 18 days (mean of 10 days) after onset.

tional supportive therapy[13]. Clinical outcomes, that is, time to improve by 1 clinical grade and time to independent walking, were assessed at 4 weeks and 6 months. In a study conducted by the French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome[14], 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 in the proportion of patients who needed assisted mechanical ventilation, a shorter time to the onset of motor recovery, and clinical factors such as time to walk with and without assistance[14]. The same group has also reported 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[15]. In 1997, a randomized, controlled, nonblinded trial included and randomized to 3 groups according to degree of disability 556 patients with Guillain-Barré 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 moderate disability were more beneficial. More than 4 treatments did not yield additional benefit in patients receiving mechanical ventilation in the group with severe disability[16]. Based on several studies of class I evidence, TPE has been established as effective treatment in the management of Guillain-Barré syndrome (Table 5). Plasma exchange is most beneficial

Table 4. Trials of therapeutic plasma exchange in Guillain-Barré syndrome

Trial	Study characteristics and design	No. of patients	Outcome
Guillain-Barré Syndrome Study Group[13]	TPE *vs*. supportive care. Single blinded	245	Improvement at 4 wk, time to improve by 1 clinical grade, time to independent walking, outcome at 6 mo in TPE group.
French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome[14]	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-Barré Syndrome[16]	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-Barré Study Group[17]	TPE (5x) *vs*. IVIG (0.4 g/kg *per* day, 5 d). Nonblinded, bias controlled.	150	Improvement by 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-Barré Syndrome Trial Group[18]	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 5. Acute inflammatory demyelinating polyneuropathy (AIDP; Guillain-Barré 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 procedures:
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.

when started within 7 days of disease onset, but is also efficacious when started after 30 days[17,18].

Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

Patients with chronic inflammatory demyelinating polyradiculoneuropathy (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 underlying diseases, including Hodgkin's disease, connective tissue diseases, inflammatory bowel disease, hepatitis, diabetes and infection with human immunodeficiency virus (HIV). Patients with monoclonal gammopathies can present similar findings. The diagnosis of CIDP is largely made clinically, but CSF may reveal elevated protein. Nerve biopsies show histologic evidence of demyelination with mononuclear infiltrate. Evidence of demyelination is also present on electrophysiological testing[7,12].

The presence of autoantibodies against various proteins and glycolipids of the peripheral nerve in samples of serum and CSF from patients with CIDP may provide a rationale for therapeutic use of TPE (Table 6). Treatment usually consists of either corticosteroid therapy or intravenous immunoglobulin (IVIG) or TPE, followed by long-term immunosuppression with cyclosporine, interferon, azathioprine, cyclo-

Table 6. Chronic inflammatory demyelinating 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 procedures:
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.

phosphamide, or other immunosuppressive therapies[5]. Therapeutic response is measured by improvement or stabilization in neurologic 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[19].

Myasthenia Gravis (MG)

Myasthenia gravis (MG) is an autoimmune syndrome caused 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. The mechanisms responsible for the loss of functional AChR that compromise or abort safe neuromuscular transmission include 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[20].

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- to 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 precipitated by other illnesses, such as 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 IVIG. 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 MG[21,22]. 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 24 hours, but may take a week. The benefits will likely subside after 2 to 4 weeks, if immunosuppressive therapies are not initiated to keep antibody levels low[5,23] (Table 7).

A randomized, controlled, 3-armed trial compared TPE with 2 regimens of IVIG in the treatment of acute exacerbations in MG. Eighty-seven patients were randomized either to undergo 3 TPE sessions or to receive IVIG (0.4 g/kg *per* day) for 3 or 5 consecutive days. As a primary outcome measure, the change in myasthenic muscular score between randomization and day 15 was chosen. Secondary end points included, among others, the decrease of anti-AChR antibody titers. Clinical improvement was observed in all patients, but no statistically significant difference in the primary end point or in the effect on anti-AChR antibodies between the 2 groups (TPE *vs.* IVIG) was documented. Adverse effects were less frequent in the IVIG group[24]. A retrospective multicenter chart review of 54 myasthenic episodes compared the two treatment modalities for myasthenic crisis. Patients received either 5 or 6 TPE of 25-45 mL/kg on alternate days or 0.4g /kg/day 3 to 5 days of IVIG. TPE resulted in significantly more improvement than IVIG in ventilatory status at 2 weeks and overall outcome at 1 month[25].

Paraproteinemic Polyneuropathies (PP)

A number of common disorders of the peripheral nervous system, termed paraproteinemic polyneuropathies (PP), are closely connected with the presence of

Table 7. Myasthenia gravis (MG)

Incidence	1 *per* 100,000/year
Category - moderate and severe - pre-thymectomy	 I I
Recommendation - moderate and severe - pre-thymectomy	 Grade 1A Grade 1C
Type of evidence - moderate and severe - pre-thymectomy	 Type I Type II-2
Procedure	TPE
Replacement fluid	Albumin
Volume treated	1 to 1.5 PV
Frequency	Daily or every other day

Duration/discontinuation/number of procedures:
A typical induction regimen consists of processing 225 mL/kg of plasma over a period of up to 2 weeks but smaller volume processing can be beneficial. The number and frequency of procedures depend upon the clinical scenario. Some patients may require long-term maintenance TPE.

excessive amounts of an abnormal immunoglobulin in the blood. These immunoglobulins can be detected by immunoelectrophoresis or the more sensitive immunofixation test. An estimated 10% of idiopathic polyneuropathies are of this type. The anomalous blood proteins are usually monoclonal (termed M protein or M spike), the product of a single clone of plasma cells, and some of them have the properties of antibodies directed at the components of the myelin or axolemma. Others have an uncertain pathophysiological role intermediate between that of proteins associated with neuropathies and that of proteins associated with lymphoproliferative disorders. The nerves may also be damaged by deposition of the amyloid byproduct of the circulating paraprotein. These neuropathies are typically associated with a monoclonal gammopathy of non-neoplastic origin, multiple myeloma, Waldenström's macroglobulinemia, osteosclerotic myeloma, primary amyloidosis, cryoglobulinemia, non-Hodgkin's lymphoma, Castleman's disease and related lymphatic diseases, and chronic leukemias[26]. The diagnosis can be established based on electrophysiological studies and the presence of monoclonal proteins. PP are most commonly seen in the setting of monoclonal gammopathy of undetermined significance (MGUS), especially IgM-MGUS. In 50% of IgM-MGUS, the specificity of IgM is myelin glycoprotein (MAG). This specificity has also been seen in WM, CLL, IgG- and IgA-MGUS. Symptoms tend to progress more rapidly in patients with IgM compared to IgA- or IgG-MGUS[5].

The principal confirmation that antinerve antibodies that are a component of a paraprotein are linked to neural damage has been derived from the detection by direct immunofluorescent staining of endoneurial deposits of immunoglobulin and complement in nerve and the induction of demyelinating neuropathy in animals by immunization with the aforementioned 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.*[27] 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 8).

Acute Disseminated Encephalomyelitis (ADEM)

Acute disseminated encephalomyelitis (ADEM) is a neurologic 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. The 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[28].

Magnetic resonance imaging (MRI) is the diagnostic imaging modality of choice for 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.

Table 8. Paraproteinemic polyneuropathies (PP)

Incidence	Monoclonal gammopathy 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 procedures: 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 the onset of symptoms).	

Table 9. 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 procedures:
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 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 the course of treatment, then response is unlikely to occur. TPE therapy consists of 3 to 6 treatments.

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 neurologic conditions that are presumed to be immune mediated. TPE works by removing the presumed offending autoantibodies as well as through immunomodulation (Table 9). 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].

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 contralateral hemispheric atrophy. The disorder usually affects children, although occasional reports of adult-onset Rasmussen's syndrome have been reported. Cumulative evidence suggests that Rasmussen's 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 directed against the glutamate receptor GluR3 have been detected in serum samples of patients with Rasmussen's encephalitis. 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 neurologic diseases, and their contribution remains unresolved. Cytotoxic CD8 T cells have been identified in the brains of affected individuals with Rasmussen's encephalitis, and it has been suggested that their direct assault on neurons underlies the 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 present with epilepsia partialis and hemi-

paresis. A combination of clinical criterion, imaging studies, electroencephalography and antibody titers will identify most cases.

Anticonvulsants are necessary, but not always effective. Based on recent pathogenic concepts, different medical treatments including IVIG, iv. methylprednisolone and oral prednisone, intraventricular interferon-α given *via* Omaya reservoir, iv. rituximab and tacrolimus have been investigated for control of epileptic and neurologic 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 with TPE in children with Rasmussen's encephalitis. This treatment was based on the demonstration of serum immunoreactivity to the GluR3 in such patients[5,29]. Despite the paucity of clinical reports, investigators in the field recommend a concerted trial of immunotherapy, including TPE (Table 10), to control seizures, mitigate functional decline, and delay the need for hemispherectomy in patients with Rasmussen's encephalitis.

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 patients, 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 the need for artificial respiration. Ptosis and diplopia can be present, but tend to be milder than in autoimmune MG. Mild to moderate autonomic dysfunction in LEMS is characterized by the presence of dry mouth, dryness of the eyes, blurred vision, impotence and constipation, 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 small cell lung cancer develop paraneoplastic cerebellar degeneration[30].

Initial management should be directed at treatment of the underlying malignancy because weakness

Table 10. 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 procedures: 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 the 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.	

Table 11. 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 procedures:
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 neurologic relapse, but the effect can be expected to last for 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 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.

frequently improves with effective cancer therapy. Apart from underlying malignancy, the management of LEMS is directed toward support immunosuppression to control production of the offending antibodies and support of acetylcholine-mediated neurotransmission to improve neurologic function. Cholinesterase inhibitors such as pyridostigmine alone, or combined with guanidine hydrochloride, that act to enhance the 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[5,23]. 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 11). TPE may be a useful adjunct to the management of patients with LEMS whose neurologic 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 short-lived unless immunosuppressant drugs are used, and additional courses are often needed to maintain benefit. Improvement may last for ever longer periods after each treatment.

Multiple Sclerosis (MS)

Multiple sclerosis (MS) 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 glycoprotein 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[31].

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 12). However, no major therapeutic effect of TPE can be expected once antibodies have been deposited *in situ* in CNS lesions. Treatment in relapsing-remitting MS includes azathioprine, IVIG, interferon β-1a, glatiramer acetate, mitoxantrone hydrochloride, natalizumab, and cyclophosphamide depending on the disease severity. TPE has not been specifically studied in relapsing-remitting MS. An appropriate 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[5,32].

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 NMO cases 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[5,33]. Within 5 years, 50% of patients lose functional vision on 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 CSF with negative oligoclonal IgG bands and leukocytosis[34]. In addition, brain MRI is not typical for MS. NMO is associated with other autoimmune diseases, such as systemic lupus erythematosus, Sjögren's disease, MG, viral infections and vaccinations. Disease course may be monophasic or relapsing. Monophasic course is associated with younger age at disease onset and equal male:female predominance. Monophasic

Table 12. 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 procedures: In acute MS unresponsive to steroids, 5 to 7 TPE procedures have a response rate of approximately 50%.	

course has a 90% 5-year survival rate. Approximately 80% of patients with NMO have relapsing course, which has a poor prognosis: 50% of patients become legally blind or wheelchair bound and 30% die from 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 it fails 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 13). 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[35]. Patients at high risk of relapse include those who are seropositive for NMO-IgG.

Conclusions

The role of TPE in the neurologic intensive care unit has changed over past 35 years. It is known that autoantibodies and immune complexes play a crucial role in many kinds of neurologic 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 patient plasma is an efficient means of treatment. In various neurologic disorders, randomized controlled studies have demonstrated the efficacy of TPE, e.g., in acute inflammatory demyelinating polyneuropathy (AIDP; Guillain-Barré 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.

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Table 13. 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 procedures:
The majority of studies performed 5 TPE on average (range 2 to 20 procedures). The patients who received TPE had lower residual disability scores (results from a retrospective cohort study). In case series, 50% to 70% of patients showed improvement after TPE, but all patients had received steroids.

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Sažetak

TERAPIJSKA IZMJENA PLAZME U NEUROLOŠKOJ JEDINICI INTENZIVNOG LIJEČENJA

P. Kes, V. Bašić-Kes, N. Bašić-Jukić i *V. Demarin*

Terapijska izmjena plazme (TIP) je dobro poznata terapijska metoda koju se rabi u liječenju brojnih imuno posredovanih neuroloških bolesti. Povoljni učinci TIP ostvaruju se uklanjanjem plazmatskih uzročnika bolesti odnosno autoantitjela, imunih kompleksa, posrednika upale, sastavnica komplementa i citokina koji imaju ključnu ulogu u nastanku neuroloških autoimunih bolesti. Randomizirana, kontrolirana istraživanja dokazala su učinkovitost TIP u liječenju slijedećih neuroloških bolesti: akutna upalna demijelinizirajuća polineuropatija (AUDP; Guillain-Barréov sindrom), kronična upalna demijelinizirajuća poliradikulopatija (KUDP), mijastenija gravis (MG) i paraproteinemijske polineuropatije (PP). U tim je bolestima TIP prihvaćena kao prvi izbor liječenja, kao jedina metoda ili u kombinaciji s drugim terapijskim metodama. Učinkovitost liječenja pomoću TIP manje je uvjerljiva u neurološkim bolestima kao što su akutni diseminirani encefalomijelitis (ADEM), kronični fokalni encefalitis (Rasmussenov encefalitis), Lambert-Eatonov mijastenični sindrom (LEMS), multipla skleroza (MS) i optički neuromijelitis (ON; Deviceva bolest). U tim bolestima TIP je prihvaćena kao drugi izbor liječenja, i to kao jedina metoda ili u kombinaciji s drugim vrstama liječenja.

Ključne riječi: *Akutni diseminirani encefalomijelitis; Akutna upalna demijelinizirajuća polineuropatija; Kronični fokalni encefalitis; Kronična upalna demijelinizirajuća poliradikulopatija; Lambert-Eatonov mijastenični sindrom; Multipla skleroza; Mijastenija gravis; Optički neuromijelitis; Paraproteinemijske polineuropatije; Terapijska izmjena plazme*