Plasmapheresis/Plasma Exchange/Therapeutic Apheresis

Number: 0285

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

A. Aetna considers plasmapheresis (PP), plasma exchange (PE), or therapeutic apheresis medically necessary for any of the following indications:
B. Acute humoral rejection of renal transplants;
C. Acute, severe neurological deficits caused by multiple sclerosis that have a poor response to treatment with high-dose glucocorticoids;
D. Anti-neutrophil cytoplasmic antibody-associated vasculitis (Wegener’s granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome) unresponsive to conventional therapy;
E. Babesiosis if member has high-grade parasitemia (greater than or equal to 10 %), severe anemia (hemoglobin less than or equal to 10 g/dL), or hepatic, pulmonary, or renal compromise (red blood cell exchange);
F. Catastrophic antiphospholipid syndrome (APS with widespread thromboembolic disease and visceral damage)
G. Chronic relapsing polynuropathy (chronic inflammatory demyelinating polynuropathy [CIDP]) with severe or life-threatening symptoms, in persons who have failed to

Policy History

Last Review 03/09/2017
Effective: 10/13/1998
Next Review: 03/08/2018

Review History

Definitions

Additional Information

Clinical Policy Bulletin Notes
respond to conventional therapy. (Note: Diagnosis of CIDP is documented by symmetric or focal neurological deficits with slowly progressive or relapsing course over 2 or more months with characteristic neurophysiological abnormalities);

H. Essential thrombocythemia (when platelet count is greater than 1,000,000/mm3) (platelet pheresis);

I. Glomerulonephritis associated with antilglomerular basement membrane antibodies and advancing renal failure or pulmonary hemorrhage;

J. Goodpasture’s syndrome (glomerulonephritis associated with antilglomerular basement membrane antibodies and advancing renal failure or pulmonary hemorrhage);

K. HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome of pregnancy, if thrombocytopenia, hemolysis, or renal failure continues to worsen 48-72 hours postpartum;

L. Hemolytic uremic syndrome;

M. Hyperglobulinemias, including (but not limited to) multiple myelomas, cryoglobulinemia, and hyperviscosity syndromes;

N. Last resort treatment of acute disseminated encephalomyelitis, where conventional treatment (including corticosteroids) has failed (i.e., severe neurological deficits have persisted after treatment with corticosteroids);

O. Last resort treatment of life-threatening rheumatoid vasculitis;

P. Last resort treatment of life-threatening systemic lupus erythematosus (SLE) when conventional therapy has failed to prevent clinical deterioration;

Q. Leukemia (leukapheresis) (for acute debulking only);

R. Myasthenia gravis, in persons with any of the following: (i) acute, short-term benefit is critical because of a sudden worsening of symptoms (such as in impending respiratory crisis), (ii) needs rapid improvement of strength before surgery or irradiation, or (iii) requires chronic intermittent treatment because of failure to respond to all other treatments;

S. Paraproteinemic demyelinating neuropathies associated
with IgA, IgG or IgM monoclonal gammopathy of undetermined significance (MGUS) (excluding multiple myeloma)

T. Pemphigus vulgaris that is resistant to standard therapy (dapsone, corticosteroids, immunosuppressants such as azathioprine or cyclosporine);

U. Pruritus from cholestatic liver disease (plasma perfusion of charcoal filters), last resort treatment in persons who have failed (unless contraindicated): bile acid resins (cholestyramine or cholesteryl), rifampin, ursodeoxycholic acid (in primary biliary cirrhosis), and opioid antagonists (naloxone, naloxone or nalmefene);

V. Recurrence of focal and segmental glomerulosclerosis in the kidney allograft;

W. Refsum's disease;

X. Renal transplantation from live donor with ABO incompatibility or positive cross-match, where a suitable non-reactive live or cadaveric donor is unavailable;

Y. Scleroderma and polymyositis, in persons who are unresponsive to conventional therapy;

Z. Severe (grades 3 to 5) Guillain Barre' syndrome (consistent with guidelines from the American Academy of Neurology, it is generally considered medically necessary to initiate PE within 2 weeks of onset of neuropathic symptoms for ambulant individuals and within 4 weeks of symptom onset for non-ambulant individuals);

AA. Severe hypercholesterolemia in persons refractory to diet and maximum drug therapy who are homozygous for familial hypercholesterolemia (LDL apheresis, also known as heparin-induced extracorporeal LDL precipitation (HELP) or dextra sulfate adsorption) with LDL levels greater than 500 mg/dL, or persons heterozygous for familial hypercholesterolemia with LDL levels greater than 300 mg/dL or greater than 200 mg/dL with documented history of coronary artery disease. (For this policy, maximum drug therapy is defined as a 6-month trial of diet plus maximum tolerated combination drug therapy (defined as a trial of drugs from at least 2 separate classes of hypolipidemic agents such as bile acid sequestrants, HMG-CoA reductase inhibitors, fibric acid derivatives, or niacin/nicotinic acids).
Documented history of coronary artery disease is defined as a history of myocardial infarction: coronary artery bypass surgery; percutaneous transluminal coronary angioplasty; alternative revascularization procedure; or angina with coronary artery disease documented by stress test. The frequency of LDL apheresis that is considered medically necessary varies, but typically averages about once every 2 weeks to obtain an intrapheresis level of low density lipoprotein cholesterol (LDL-C) of 120 mg/dL or less. It may be considered medically necessary to treat individuals with homozygous familial hypercholesterolemia more frequently);

AA. Sickle cell disease (therapeutic cytopheresis);
AB. Solid organ transplant from donor with positive cross-match, where a suitable non-reactive donor is unavailable;
AC. Treatment of neuromyelitis optica (Devic's syndrome) that is refractory to glucocorticoids;
AD. Treatment of thrombotic thrombocytopenic purpura (TTP) or microangiopathic hemolytic anemia
AE. Treatment of transverse myelitis when corticosteroid treatment has failed.
AF. Waldenstrom's macroglobulinemia, prophylactic treatment in persons with IgM greater than or equal to 5000 mg/dL while on rituximab or ofatumumab mg/dL, to avoid aggravation of serum viscosity on the basis of IgM flare related to rituximab or ofatumumab.

II. Aetna considers PP/PE or therapeutic apheresis experimental and investigational for all other indications, including the following conditions (not an all-inclusive list) because the medical literature does not support the value of PP/PE for these indications:

A. Acute pancreatitis related to hyperlipidemia;
B. Alzheimer's disease;
C. Amyotrophic lateral sclerosis;
D. Anti-MAG neuropathy;
E. Autoimmune inner ear disease;
F. Bullous pemphigoid;
G. Chronic fatigue syndrome;
H. Chronic progressive or secondary progressive multiple sclerosis (maintenance therapy);
I. Chronic urticaria;
J. Hashimoto's encephalopathy;
K. Hypertriglyceridemia;
L. Idiopathic myopathy;
M. Idiopathic progressive polyneuropathy
N. Idiopathic sudden hearing loss;
O. Idiopathic thrombocytopenic purpura;
P. Lupus nephritis;
Q. Macular degeneration;
R. Miller Fisher syndrome;
S. Multifocal motor neuropathy (MMN);
T. Multiple myeloma;
U. Necrobiotic xanogranulomatous skin disorder;
V. Nephrogenic systemic fibrosis;
W. Neuropathy associated with immunoglobulin M gammopathy;
X. Neuropsychiatric symptoms associated with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS);
Y. Obsessive-compulsive disorder;
Z. Optic neuritis;
AA. Paraneoplastic syndromes including Eaton-Lambert syndrome and paraproteinemic polyneuropathy;
AB. Parkinson’s disease;
AC. Postural orthostatic tachycardia syndrome;
AD. Psoriasis;
AE. Pulmonary alveolar proteinosis;
AF. Raynaud’s phenomenon;
AG. Reducing perioperative blood transfusion;
AH. Regional enteritis;
AI. Sepsis or septic shock;
AJ. Status epilepticus;
AK. Stiff-person syndrome;
AL. Sydenham's chorea.

III. Aetna considers high density lipoprotein (HDL) delipidation and plasma re-infusion for acute coronary syndrome and all other indications experimental and investigational because its
efectiveness has not been established.

See also [CPB 0241 - Extracorporeal Photochemotherapy (Photopheresis) (0241.html)] and [CPB 0355 - Extracorporeal Immunoadsorption (Proserba Column) (../300_399/0355.html)]

Background
The terms plasmapheresis (PP) and plasma exchange (PE) are often used interchangeably, but when properly used, denote different procedures. Plasmapheresis refers to a procedure in which the plasma is separated from the blood either by centrifugation or membrane filtration. Once separated the plasma can be manipulated in a variety of ways. Plasma exchange refers to discarding the plasma totally and substituting a replacement fluid. In this assessment PP/PE will be used to describe the combined procedure.

Therapeutic plasmapheresis (also known as platepheresis or plasma exchange) is performed to remove toxic elements from the bloodstream. An intravenous catheter (small tube) is placed into a vein and connected to a machine (cell separator) via plastic tubing. Blood is pumped through the tubing into the machine where it is separated into red blood cells, white blood cells and plasma. The plasma is then discarded while the other components are combined with a plasma substitute and reinfused into the individual.

Randomized trials have shown that PP/PE is a safe and effective treatment of Guillain Barre syndrome (GBS), particularly if instituted early in the course of disease. Hughes et al (2007) reported on a systematic evidence review of immunotherapy for GBS. In 4 trials with altogether 585 severely affected adult participants, those treated with PP/PE improved significantly more on this scale 4 weeks after randomization than those who did not, weighted mean difference (WMD) -0.89 (95 % confidence interval (CI): -1.14 to -0.63). In 5 trials with altogether 582 participants, the improvement on the disability grade scale with intravenous immunoglobulin (IVIG) was very similar to that with PP/PE, WMD -0.02 (95 % CI: -0.25 to 0.20). There was also no significant difference between IVIG and PP/PE for any of the other
outcome measures. In 1 trial with 148 participants, following PP/PE with IVIG did not produce significant extra benefit.

Less conclusive information is available regarding PP/PE as a treatment of chronic inflammatory demyelinating polyneuropathy (CIDP); however, this therapy is widely accepted by the medical community. In a Cochrane systematic evidence review, Mehndiratta et al (2004) identified evidence from 2 small trials showing that PP/PE provides significant short-term benefit in about 2/3 of patients with CIDP but rapid deterioration may occur afterwards. The authors reported that adverse events related to difficulty with venous access, use of citrate and hemodynamic changes are not uncommon. The authors noted that a separate Cochrane evidence review found no significant difference in the benefit from PP/PE and IVIG.

Although PP/PE is an accepted treatment of GBS and CIDP, its mechanism of action is still poorly understood. It is presumed that the symptomatology of these diseases is immune mediated and that PP/PE will remove the pathogenic immune circulating factors. However, the specific immune factors responsible for the disease have not been identified. Thus PP/PE is a non selective approach, eliminating the entire plasma. It should be noted that both these therapies are primarily symptomatic; they do not directly address the production of the pathogenic factors. Guillain Barre syndrome is an acute self-limited disease; therefore therapy is needed only for a limited period of time. On the other hand, CIDP is a chronic disease, and PP/PE or IVIG is often needed on a chronic basis. Physicians titrate the frequency of therapies to the recurrence of symptomatology.

Controlled clinical trials have failed to validate the effectiveness of PP/PE as a treatment of systemic lupus erythematosus (SLE), polymyositis/dermatomyositis and rheumatoid arthritis. Early small case series of PP/PE as a treatment of rheumatoid vasculitis have not been followed-up with larger controlled studies and no conclusions can be reached as to its effectiveness. There is minimal information on other autoimmune rheumatic diseases.

There was early enthusiasm for PP/PE as a treatment of chronic
rheumatic diseases. The rationale was based on the fact that humoral factors, such as immunoglobulins or circulating immune complexes, can accumulate in the plasma in rheumatic diseases. It was hypothesized that the removal of these factors by PP/PE would correct the clinical abnormality. While PP/PE can indeed lower the serologic level of various disease markers such as circulating immune complexes, anti-DNA antibodies, cryoglobulins or rheumatoid factor, a positive clinical effect on symptomatology has not been demonstrated in clinical trials. The discrepancy may be related to the fact that PP/PE is essentially a symptomatic treatment. Although PP/PE may remove circulating immunoglobulins and immune complexes, their local production may persist unabated.

In a systematic review of randomized controlled trials of PP/PE, Shehata et al (2002) identified 8 studies (n = 192), 6 of rheumatoid arthritis and 2 studies of progressive systemic sclerosis (scleroderma). Plasmapheresis/plasma exchange was not as effective as adjunctive therapy in patients with rheumatoid arthritis. In addition, there were no benefits for the use of PP/PE in patients with progressive systemic sclerosis. In 2 studies (n = 140) the addition of PP/PE was not shown to benefit disease activity, the relapse rate, or the number of deaths in patients with polyarteritis nodosa and Churg-Strauss syndrome. In 7 studies (n = 268), therapeutic PP/PE has not been found to have an additive benefit in SLE patients with active disease or renal disease.

Choy et al (2005) reported on a systematic evidence review of immunotherapy for dermatomyositis and polymyositis. The investigators reported that 2 randomized placebo-controlled trials assessing PE, leukapheresis and azathioprine produced negative results. The authors concluded that this systematic review highlights the lack of high quality randomized controlled trials that assess the efficacy and toxicity of immunosuppressants in inflammatory myositis.

Franc et al (2005) reviewed the evidence from randomized controlled clinical trials for treatments for lupus nephritis. The investigators found, based upon a review of clinical trials, that the current use of cyclophosphamide combined with steroids remains
the best option to preserve renal function in proliferative lupus nephritis. The authors found no benefit with addition of PE to cyclophosphamide or azathioprine plus steroids for mortality (risk ratio [RR] 0.71, 95% CI: 0.50 to 1.02), doubling of serum creatinine (RR 0.17, 95% CI: 0.02 to 1.26) or end-stage renal failure (RR 1.24, 95% CI: 0.60 to 2.57).

Fisher syndrome is one of the regional variants of GBS, characterized by impairment of eye movements (ophthalmoplegia), incoordination (ataxia) and loss of tendon reflexes (areflexia). It can occur in more limited forms, and may overlap with GBS. A Cochrane systematic evidence review found no randomized or non-randomized prospective controlled trials of immunotherapy in Fisher Syndrome or related disorders (Overell et al, 2007). In the largest study of PP/PE for Miller Fischer syndrome reported to date, Mori et al (2002) reported on a retrospective analysis of 50 patients with Miller Fisher syndrome to determine its effect on speed of recovery. The investigators found no effect of PP/PE on measures of speed of recovery.

There are no proven effective therapies for neuromyelitis optica. Based on experimental and pathological evidence, it is thought that immunoglobulins and complement deposition are likely to play a role in the pathogenesis of neuromyelitis optica. Glucocorticoids are typically used to treat cases acutely and may be beneficial. Azathioprine has been used for subsequent attacks. Information from the National Institute of Neurological Disorders and Stroke (2007) states that PE may be tried in patients who do not respond to glucocorticoids. In an uncontrolled case series, 6 of 10 patients with neuromyelitis optica treated with PE showed moderate or marked improvement (Keegan et al, 2002). A double-blind cross-over study of PP versus sham exchanges found that PP (7 exchanges of approximately 55 ml/kg administered every other day) was beneficial treating exacerbations of demyelinating disease (including neuromyelitis optica) that are not responsive to methylprednisolone (Weinshenker et al, 1999).

This study was a retrospective analysis of 7 patients with MMN, who underwent 4 to 18 sessions of PE. Clinical response, electrophysiological parameter and anti-ganglioside antibody titers were reviewed. Two patients, who had anti-ganglioside antibodies, exhibited transient clinical responses to PE, manifested by improved neurological function. Whereas electrophysiological parameters continued to worsen in all patients, anti-ganglioside antibody titers declined during PE, but increased after PE. The authors concluded that PE is of limited therapeutic value in patients with MMN, who do not respond to established treatment options. It may only be useful as an adjunctive treatment in a subset of patients. The transient decrease of anti-ganglioside-antibodies titers suggested that pathogenic humoral factors in MMN are only temporarily reduced. Further, PE treatment alone is insufficient to prevent axons from continuing degeneration, which may explain the failure of PE to substantially influence the disease course of patients with MMN.

In a Cochrane review, Micheal et al (2009) evaluated the benefits and harms of different interventions for hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) separately in patients of all ages. The authors concluded that PE with fresh frozen plasma is still the most effective treatment available for TTP. For patients with HUS, supportive therapy including dialysis is still the most effective treatment. All studies in HUS have been conducted in the diarrheal form of the disease. There were no randomized controlled trials evaluating the effectiveness of any interventions on patients with atypical HUS who have a more chronic and relapsing course.

The Multiple Sklerose Therapie Konsensus Gruppe (2006) stated that the monoclonal antibodies provide considerable improvement of treatment for multiple sclerosis (MS), but their use in basic therapy is restricted by their side effect profile. Thus, natalizumab is only approved for monotherapy after basic treatment has failed or for rapidly progressive relapsing-remitting MS. In contrast, long-term data on recombinant beta-interferons and glatiramer acetate (Copaxone) show that even after several years no unexpected side effects occur and that a prolonged
therapeutic effect can be assumed which correlates with the dose or frequency of treatment. Recently IFN-beta1b (Betaferon) was approved for prophylactic treatment after the first attack (clinically isolated syndrome, CIS). During treatment with beta-interferons, neutralizing antibodies can emerge with possible loss of effectiveness. In contrast, antibodies play no role in treatment with glatiramer acetate. During or after therapy with mitoxantrone, serious side effects (cardiomyopathy, acute myeloid leukemia) appeared in 0.2 to 0.4% of cases. Plasmapheresis is limited to individual curative attempts in escalating therapy of a severe attack. According to the revised McDonald criteria, the diagnosis of MS can be made as early as the occurrence of the first attack.

Tackenberg et al (2007) stated that the natural course of MS is probably more favorable than previously assumed years ago. Since the introduction of interferons in Germany, the establishment and further development of new diagnostic criteria (McDonald criteria), the causal and symptomatic treatment possibilities and initiation of therapy early in the course of the disease have led to a considerable change in the treatment of MS. Attacks of MS are usually treated with the intravenous administration of high-dosed steroids. When the attack symptoms do not sufficiently subside, PP can be considered. For long-term treatment of MS, beta interferon, glatirameracetate and natalizumab are available as basic causal therapy and natalizumab and mitoxantrone are available for escalation therapy. Frequently occurring spasticity, chronic fatigue syndrome, depression, cognitive disturbances, incontinence, pain, ataxia and sexual disorders must be treated symptomatically. Overall, the outpatient treatment of MS is complex and should be carried out with close co-operation between the family doctor, neurological practices and outpatient departments specialized in treating MS.

Oh et al (2008) noted that B-cells and humoral immunity have been implicated in the pathogenesis of MS. The most common pattern of demyelinating pathology in MS is associated with the deposition of antibodies and the activation of complement, as well as T-cells and macrophages. Plasmapheresis has been found
to be an efficient therapeutic approach in patients with this type of pathological lesion.

Matsui (2008) noted that Japanese patients with relapsing-remitting multiple sclerosis (RRMS) consists of 2 groups. One is opticospinal form (OSMS), in which major neurological symptoms derive from optic neuritis and myelitis, and the other is conventional form (CMS) that shares similar genetical and clinical features with western type of MS. Patients with OSMS tend to experience disease relapses more frequently with the resultant severer neurological deficit than CMS ones. Both OSMS and CMS patients are treated with intravenous high-dose methylprednisolone in acute exacerbations, and PP may be considered for those who do not respond to repeated intravenous steroids. For prevention of disease relapse, interferon-beta is effective; however, patients with long spinal cord lesion extending over 3 vertebral segments should be followed-up with caution, as this finding indicates a risk of treatment failure.

Ohji and Nomura (2008) discussed steroid pulse therapy and apheresis therapy indicated for the treatment of MS. In the basic treatment course for MS, steroid pulse therapy is a 1st-line treatment for RR-MS in the course of the exacerbation, and apheresis therapy is performed in refractory cases. Treatment strategies for chronic progressive MS are not to be established. Steroid pulse therapy has been established as a treatment for MS in the active phase through randomized controlled trials (RCT). Apheresis therapy includes PP and cytapheresis, and PP includes PE and immunoadsorption plasmapheresis (IAPP). Plasma exchange and IAPP are performed for MS treatment. The former has been established as a useful treatment for active phase MS. The efficacy of IAPP has been frequently reported, but no reports have been based on RCT.

Schroder et al (2009) stated that apheresis is a general term that describes removal of abnormal blood constituents by extracorporeal blood purification methods. To date, therapeutic PE is the most common apheresis procedure. Here, plasma is separated from corpuscular blood constituents and replaced with
a substitution fluid. In contrast to immunoadsorption, PE is a non-specific treatment modality with elimination of the entire plasma. The therapeutic effect is based on the removal of circulating, pathogenic immune factors including autoantibodies. Currently, PE is used for treatment of several immune-mediated neurological disorders. While first experiences relate to acute life-threatening conditions, such as treatment of GBS or myasthenic crisis, therapeutic success was also shown in chronic diseases where immunosuppressive therapy is often required for long-term management. Plasma exchange has been applied successfully in CIDP, paraproteinemic polyneuropathy, stiff person syndrome, and may also be tried in several diseases of paraneoplastic origin. In recent years, PE was also established as an escalation therapy for steroid-unresponsive relapses of MS, and thus has gained more widespread attention.

Olek (2009) stated that PE may be beneficial in patients with acute central nervous system (CNS) inflammatory demyelinating disease who do not respond to glucocorticoid therapy. In the only formally reported clinical trial, 22 patients with CNS demyelinating disease (12 with MS) were randomly assigned to either active PE or sham treatment, with a total of 7 treatments, given every 2 days over 14 days. Moderate or greater improvement in neurologic disability occurred during 8 of 19 (42 %) courses of active treatment compared with 1 of 17 (6 %) courses of sham treatment. Improvement occurred early in the course of treatment and was sustained on follow-up. However, 4 of the patients who responded to the active treatment experienced new attacks of demyelination during 6 months of follow-up. Given these data, the author suggested treatment with PE for patients with acute, severe neurologic deficits caused by MS who have a poor response to treatment with high-dose glucocorticoids.

Ruprecht and colleagues (2004) reviewed a series of 10 consecutive patients treated with PE for acute, severe optic neuritis (ON) largely unresponsive to previous high-dose intravenous glucocorticosteroids. Plasma exchange was associated with an improvement of visual acuity according to the study criteria in 7 of 10 patients. On follow-up, 3
of these patients continued to improve, 2 remained stable, and 2 had worsened again. The authors noted that PE may be beneficial as an escalating treatment in a subset of patients with severe ON; but a controlled trial is needed. Furthermore, in a review on ON, Osborne and Volpe (2009) stated that data on the use of PE in the treatment of patients with ON are too scarce to make any recommendations.

Boada-Rovira (2010) noted that results from a pilot study and its 2-year extension performed on patients with mild or moderate Alzheimer’s disease (AD) revealed a tendency towards clinical stabilization after a PP program with PE with therapeutic albumin Human albumin Grifols 5 %. Plasma levels of alphabeta(40) and alphabeta(42) presented a saw-tooth pattern associated to PE. These findings encouraged a new randomized, controlled, parallel, blind study to confirm the previous working hypotheses, i.e., that alphabeta(40) and alphabeta(42) concentrations in plasma were modified pre- and post-PP with human albumin Grifols 5 % and, in the clinical area, that the cognitive capabilities of patients could be stabilized or even improved. Other aims of the study were focused on neuroimaging evaluation of structural and functional changes in the brain the by means of magnetic resonance and single-photon emission computerized tomography. Preliminary results from the randomized study performed after a follow-up of 1 year of the first 29 patients (80 % of the recruited) show a clear difference between the treated and the control groups with regard to the levels of alphabeta(40), both in plasma and in cerebrospinal fluid, that are associated with the PE. This pattern is not so evident for alphabeta(42).

Regarding cognitive performance, the treated group scored better than the control group after the period study, according to the evaluation performed by using the Mini-Mental State Examination (MMSE) and AD Assessment Scale-Cognitive (ADAS-Cog) tests. The authors concluded that these preliminary results suggested that PP with PE with human albumin Grifols 5 % may have a promising future as a treatment of mild-moderate AD.

In a Cochrane review, Kirtschig et al (2010) evaluated treatments for bullous pemphigoid (BP); RCTs of treatments for subjects with immunofluorescence-confirmed BP were included in this
analysis. At least 2 authors evaluated the studies for the inclusion criteria, and extracted data independently. A total of 10 RCTs (with a total of 1,049 participants) of moderate-to-high risk of bias were selected. All studies involved different comparisons, none had a placebo group. In 1 trial PE plus prednisone gave significantly better disease control at 1 month (0.3 mg/kg: RR 18.78, 95 % CI: 1.20 to 293.70) than prednisone alone (1.0 mg/kg: RR 1.79, 95 % CI: 1.11 to 2.90), while another trial showed no difference in disease control at 6 months. No differences in disease control were seen for different doses or formulations of prednisolone (1 trial each), for azathioprine plus prednisone compared with prednisone alone (1 trial), for prednisolone plus azathioprine compared with prednisolone plus PE (1 trial), for prednisolone plus mycophenolate mofetil or plus azathioprine (1 trial), for tetracycline plus nicotinamide compared with prednisolone (1 trial). Chinese traditional medicine plus prednisone was not effective in 1 trial. There were no significant differences in healing in a comparison of a standard regimen of topical steroids (clobetasol) with a milder regimen (RR 1.00, 95 % CI: 0.97 to 1.03) in 1 trial. In another trial, clobetasol showed significantly more disease control than oral prednisolone in people with extensive and moderate disease (RR 1.09, 95 % CI: 1.02 to 1.17), with significantly reduced mortality and adverse events (RR 1.06, 95 % CI: 1.00 to 1.12). The authors concluded that very potent topical steroids are effective and safe treatments for BP, but their use in extensive disease may be limited by side-effects and practical factors. Milder regimens (using lower doses of steroids) are safe and effective in moderate BP. Starting doses of prednisolone greater than 0.75 mg/kg/day do not give additional benefit, lower doses may be adequate to control disease and reduce the incidence and severity of adverse reactions. The effectiveness of adding PE, azathioprine or mycophenolate mofetil to corticosteroids, and combination treatment with tetracycline and nicotinamide needs further investigation.

In January 2011, the American Academy of Neurology (AAN) published a new guideline on PP in neurologic disorders (Cortese et al, 2011). It states that PP/PE can be used as 2nd-line treatment of steroid-resistant exacerbations in relapsing forms of
MS. Moreover, PP is established as ineffective and should not be offered for chronic or secondary progressive MS. The guideline also stated that PP is probably not effective and should not be considered for neuropathy associated with immunoglobulin M gammopathy.

The AAN (Scott et al, 2011) evaluated the evidence for diagnostic tests and therapies for transverse myelitis (TM) and made evidence-based recommendations. A review of the published literature from 1966 to March 2009 was performed, with evidence-based classification of relevant articles. Level B recommendations: Neuromyelitis optica (NMO)-immunoglobulin G (IgG) antibodies should be considered useful to determine TM cause in patients presenting with clinical acute complete transverse myelitis (ACTM) features. The presence of NMO-IgG antibodies (aquaporin-4-specific antibodies) should be considered useful in determining increased TM recurrence risk. Level C recommendations: In suspected TM, distinction between ACTM or acute partial transverse myelitis may be considered useful to determine TM etiology and risk for relapse (more common with APTM). Age and gender may be considered useful to determine etiology in patients presenting with TM syndrome, with spinal infarcts seen more often in older patients and more female than male patients having TM due to MS. Brain MRI characteristics consistent with those of MS may be considered useful to predict conversion to MS after a first partial TM episode. Longer spinal lesions extending over more than 3 vertebral segments may be considered useful in determining NMO versus MS. Cerebrospinal fluid examination for cells and oligoclonal bands may be considered useful to determine the cause of the TM syndrome. Plasma exchange may be considered in patients with TM who fail to improve after corticosteroid treatment. Rituximab may be considered in patients with TM due to NMO to decrease the number of relapses. Level U recommendations: There is insufficient evidence to support or refute the efficacy of other TM therapies or the usefulness of ethnicity to determine the cause of a subacute myelopathy.

An UpToDate review on “Clinical manifestations, diagnosis, treatment, and prevention of babesiosis” (Gelfand and Vannier,
2012) states that “Partial or complete red cell exchange transfusion is appropriate for patients with high-grade parasitemia (≥10 percent), severe anemia (hemoglobin ≤10 g/dL), or pulmonary, renal, or hepatic compromise .... Exchange transfusion is intended to clear the systemic compartment of infected red blood cells, to remove inflammatory mediators and toxic by-products of cell lysis, and to correct anemia. Management of exchange transfusion should be handled in close consultation with experts in hematology and pheresis. A single red cell exchange may be adequate, but multiple exchanges may be needed. A 90 percent reduction in parasitemia has been proposed as the desired target of red blood cell exchange in babesiosis. The volume of allogeneic red cells required to achieve such reduction in parasitemia is predicted to be 2.5 times the estimated volume of recipient’s red blood cells”.

In a Cochrane review, Carless et al (2011) examined the evidence for the efficacy of platelet-rich plasmapheresis (PRP) in reducing peri-operative allogeneic red blood cell (RBC) transfusion, and the evidence for any effect on clinical outcomes such as mortality and re-operation rates. These investigators identified studies by searching MEDLINE (1950 to 2009), EMBASE (1980 to 2009), the Cochrane Library (Issue 1, 2009), the Internet (to March 2009) and the reference lists of published articles, reports, and reviews. Controlled parallel group trials in which adult patients, scheduled for non-urgent surgery, were randomized to PRP, or to a control group that did not receive the intervention were selected for analysis. Primary outcomes measured were: the number of patients exposed to allogeneic RBC transfusion, and the amount of RBC transfused. Other outcomes measured were: the number of patients exposed to allogeneic platelet transfusions, fresh frozen plasma, and cryoprecipitate, blood loss, re-operation for bleeding, post-operative complications (thrombosis), mortality, and length of hospital stay. Treatment effects were pooled using a random-effects model. A total of 22 trials of PRP were identified that reported data for the number of patients exposed to allogeneic RBC transfusion. These trials evaluated a total of 1,589 patients. The relative risk (RR) of exposure to allogeneic blood transfusion in those patients randomized to PRP was 0.73 (95 % CI: 0.59 to 0.90), equating to a relative risk reduction (RRR)
of 27 % and a risk difference (RD) of 19 % (95 % CI: 10 % to 29 %). However, significant heterogeneity of treatment effect was observed (p < 0.00001; I² = 79 %). When the 4 trials by Boldt were excluded, the RR is 0.76 (95 % CI: 0.62 to 0.93). On average, PRP did not significantly reduce the total volume of RBC transfused (weighted mean difference [WMD] -0.69, 95 %CI: -1.93 to 0.56 units). Trials provided inadequate data regarding the impact of PRP on morbidity, mortality, and hospital length of stay. Trials were generally small and of poor methodological quality. The authors concluded that although the results suggested that PRP is effective in reducing allogeneic RBC transfusion in adult patients undergoing elective surgery, there was considerable heterogeneity of treatment effects and the trials were of poor methodological quality. They stated that the available studies provided inadequate data for firm conclusions to be drawn regarding the impact of PRP on clinically important endpoints.

The American Academy of Child and Adolescent Psychiatry’s practice parameter for the assessment and treatment of children and adolescents with obsessive-compulsive disorder (AACAP, 2012) stated that “Therapeutic plasma exchange and intravenous immunoglobulin remain experimental interventions with substantial risk and potential morbidity”.

Hanna and Wong (2013) stated that sepsis remains an important challenge in pediatric critical care medicine. These investigators provided an appraisal of adjunctive therapies for sepsis and highlighted opportunities for meeting selected challenges in the field. The authors stated that future clinical studies should address long-term and functional outcomes as well as acute outcomes. Potential adjunctive therapies such as corticosteroids, hemo-filtration, hemo-adsorption, and PP may have important roles, but still require formal and more rigorous testing by way of clinical trials.

Low high-density lipoprotein (HDL) is associated with increased risk of cardiovascular disease. Plasma selective delipidation converts alphaHDL to prebeta-like HDL, the most effective form of HDL for lipid removal from arterial plaques.
Tardif et al (2007) investigated the effects of reconstituted HDL on plaque burden as assessed by intra-vascular ultrasound (IVUS). Between July 2005 and October 2006, a total of 183 patients had a baseline IVUS examination and of those, 145 had evaluable serial IVUS examinations after 6 weeks. A total of 60 patients were randomly assigned to receive 4 weekly infusions of placebo (saline); 111 to receive 40 mg/kg of reconstituted HDL (CSL-111); and 12 to receive 80 mg/kg of CSL-111. The primary efficacy parameter was the percentage change in atheroma volume. Nominal changes in plaque volume and plaque characterization index on IVUS and coronary score on quantitative coronary angiography were also pre-specified end-points. The higher-dosage CSL-111 treatment group was discontinued early because of liver function test abnormalities. The percentage change in atheroma volume was -3.4 % with CSL-111 and -1.6 % for placebo (p = 0.48 between groups, p < 0.001 versus baseline for CSL-111). The nominal change in plaque volume was -5.3 mm3 with CSL-111 and -2.3 mm3 with placebo (p = 0.39 between groups, p < 0.001 versus baseline for CSL-111). The mean changes in plaque characterization index on IVUS (-0.0097 for CSL-111 and 0.0128 with placebo) and mean changes in coronary score (-0.039 mm for CSL-111 and -0.071 mm with placebo) on quantitative coronary angiography were significantly different between groups (p = 0.01 and p = 0.03, respectively). Administration of CSL-111 40 mg/kg was associated with mild, self-limiting transaminase elevation but was clinically well-tolerated. The authors concluded that short-term infusions of reconstituted HDL resulted in no significant reductions in percentage change in atheroma volume or nominal change in plaque volume compared with placebo, but did result in statistically significant improvement in the plaque characterization index and coronary score on quantitative coronary angiography. They stated that elevation of HDL remains a valid target in vascular disease and further studies of HDL infusions including trials with clinical end-points are needed.

Waksman et al (2010) examined if serial autologous infusions of selective HDL delipidated plasma are feasible and well-tolerated in patients with acute coronary syndrome (ACS). Patients with ACS undergoing cardiac catheterization with greater than or equal to 1 non-obstructive native coronary artery atheroma were
randomized to either 7 weekly HDL selective delipidated or control plasma apheresis/reinfusions. Patients underwent IVUS evaluation of the target vessel during the catheterization for ACS and up to 14 days following the final apheresis/reinfusion session. Two-dimensional gel electrophoresis of delipidated plasmas established successful conversion of alphaHDL to prebeta-like HDL. The trial was complete with 28 patients randomized. All reinfusion sessions were tolerated well by all patients. The levels of prebeta-like HDL and alphaHDL in the delipidated plasma converted from 5.6 % to 79.1 % and 92.8 % to 20.9 %, respectively. The IVUS data demonstrated a numeric trend toward regression in the total atheroma volume of -12.18 +/- 36.75 mm(3) in the delipidated group versus an increase of total atheroma volume of 2.80 +/- 21.25 mm(3) in the control group (p = 0.268). The authors concluded that in ACS patients, serial autologous infusions of selective HDL delipidated plasma are clinically feasible and well-tolerated. They stated that this therapy may offer a novel adjunct treatment for patients presenting with ACS. Moreover, they stated that further investigation is needed to determine its ability to reduce clinical cardiovascular events.

An UpToDate review on “HDL metabolism and approach to the patient with abnormal HDL-cholesterol levels” (Rosenson and Durrington, 2013) cited the study by Tardif et al (2007) and listed infusion of reconstituted HDL as an investigational therapy. Moreover, the review does not mention HDL delipidation and plasma re-infusion as a therapeutic option.

Guidelines from the National Comprehensive Cancer Network (NCCN, 2014) on Waldenstrom’s Macroglobulinemia/Lymphoplasmacytic Lymphoma state that plasmapheresis should be performed for patients with symptomatic hyperviscosity, and before treatment with rituximab or ofatumumab containing regimen in patients with patients with IgM greater than or equal to 5000 mg/dL on rituximab-containing therapy to avoid aggravation of serum viscosity on the basis of rituximab-containing IgM flare. The guidelines state that rituximab or ofatumumab may also be held in patients with elevated serum IgM levels for initial treatment cycles.
Current guidelines recommend plasmapheresis for acute hemoral rejection of renal transplants. Kidney Disease: Improving Global Outcomes (KDIGO) clinical guidelines suggest treating antibody-mediated acute rejection with one or more of the following alternatives, with or without corticosteroids (2C recommendation): plasma exchange; intravenous immunoglobulin; anti-CD20 antibody; or lymphocyte-depleting antibody (Kasiske, et al., 2009). European Association of Urology guidelines on renal transplantation (Kälble, et al., 2009) state that treatment of acute humoral rejection of a renal transplant may include steroid bolus therapy, conversion to tacrolimus, antibody elimination and intravenous immunoglobulin (Grade B recommendation). Guidelines from the Renal Association (Baker, et al., 2011) suggest that antibody mediated rejection should be treated with one or more of the following modalities: steroids; plasma exchange; intravenous immunoglobulin; anti-CD20 antibody; or lymphocyte-depleting antibody (2C recommendation).

Brouet et al (1990) stated that monoclonal IgM from patients with peripheral neuropathy react in nearly 80 % of the cases with some components of myelin. The main target is myelin associated glycoprotein (50 % of the cases); several types of glycolipids or gangliosides have been identified as the reactive antigen in the other cases. Anti-MAG IgM shared little cross reactive idiotopes. Only primate anti-sera identified a combining site related public idiotope. In fact, these IgM used various light and heavy chains belonging to different variability subgroups. The authors concluded that the preliminary results of an ongoing trial aimed to establish the benefit of plasmapheresis in these patients.

Rimmer et al (2014) evaluated the safety and effectiveness of PE in patients with sepsis. These investigators searched MEDLINE, EMBASE, CENTRAL, Scopus, reference lists of relevant articles, and grey literature for relevant citations. They included RCTs comparing PE or plasma filtration with usual care in critically ill patients with sepsis or septic shock. Two reviewers independently identified trials, extracted trial-level data and performed risk of bias assessments using the Cochrane Risk of
Bias tool. The primary outcome was all-cause mortality reported at longest follow-up. Meta-analysis was performed using a random-effects model. Of 1,957 records identified, these researchers included 4 unique trials enrolling a total of 194 patients (1 enrolling adults only, 2 enrolling children only, 1 trial enrolling adults and children). The mean age of adult patients ranged from 38 to 53 years (n = 128) and the mean age of children ranged from 0.9 to 18 years (n = 66). All trials were at unclear to high risk of bias. The use of PE was not associated with a significant reduction in all-cause mortality (RR 0.83, 95 % CI: 0.45 to 1.52, I2 60 %). In adults, PE was associated with reduced mortality (RR 0.63, 95 % CI: 0.42 to 0.96; I2 0 %), but was not in children (RR 0.96, 95 % CI: 0.28 to 3.38; I2 60 %). None of the trials reported ICU or hospital lengths of stay. Only 1 trial reported adverse events associated with PE including 6 episodes of hypotension and 1 allergic reaction to fresh frozen plasma. The authors concluded that insufficient evidence exists to recommend PE as an adjunctive therapy for patients with sepsis or septic shock. They stated that rigorous RCTs evaluating clinically relevant patient-centered outcomes are needed to evaluate the impact of PE in this condition.

Hildebrand et al (2014) stated that therapeutic PE (TPE) has been used as adjunctive therapy for various kidney diseases dating back to the 1970s. In many cases, support for TPE was on mechanistic grounds given the potential to remove unwanted large molecular-weight substances such as autoantibodies, immune complexes, myeloma light chains, and cryoglobulins. More recently, growing evidence from RCTs, meta-analyses, and prospective studies has provided insights into more rational use of this therapy. These investigators described the role of TPE for the 6 most common kidney indications in the 2013 Canadian Apheresis Group (CAG) registry and the evidence that underpinned current recommendations and practice. These kidney indications include (i) thrombotic microangiopathy, (ii) antiglomerular basement membrane disease, (iii) anti-neutrophil cytoplasmic antibody-associated vasculitis, (iv) cryoglobulinemia, (v) recurrence of focal and segmental glomerulosclerosis in the kidney allograft, and (vi) kidney transplantation.
The Society of Obstetricians and Gynecologists of Canada’s guideline on “Treatment of the hypertensive disorders of pregnancy” (Magee et al, 2014) states that “The following interventions were considered but not recommended or there was insufficient evidence to make a recommendation: plasma exchange or plasmapheresis for HELLP syndrome .... The guideline developers recommend against plasma exchange or plasmapheresis for hemolysis, elevated liver enzymes, low platelets syndrome, particularly within the first 4 days postpartum”. SOGC guidelines note insufficient evidence for plasma exchange or plasmapheresis, noting that observational studies have suggested improved hematological and biochemical indicators, but small RCTs have found no maternal or perinatal outcome improvement.

Also, an UpToDate review on “HELLP syndrome” (Sibai, 2014) does not mention plasmapheresis, plasma exchange, or therapeutic apheresis as therapeutic options.

By contrast, guidelines from the American Society of Hematology (Rajasekhar, et al., 2013) recommend the use of plasma exchange in HELLP syndrome if thrombocytopenia, hemolysis, or renal failure continues to worsen 48 to 72 hours postpartum.

A review by Gernsheimer, et al. (2013) recommends plasma exchange if thrombocytopenia, hemolysis, or renal failure continues to worsen 48-72 hours postpartum and differentiating between preeclampsia/HELLP/AFLP and thrombotic thrombocytopenic purpura (TTP)/atypical hemolytic uremic syndrome that can follow a normal pregnancy becomes difficult, if not impossible. The authors noted that several case series suggest that the use of plasma exchange treatment may improve the outcome of both severe HELLP and AFLP.

Pagano et al (2014) noted that the effectiveness of TPE in stiff-person syndrome (SPS) is unclear. These researchers performed a retrospective analysis of patients diagnosed with SPS who underwent TPE and a systematic literature review. A total of 9 patients with the presumptive diagnosis of SPS who underwent TPE were identified. The mean age was 55 years (range of 34 to
72 years) and 78 % (n = 7) were female. Anti-GAD65 was present in 89 % (n = 8) of the patients (range of 1.9 to 40,000 U/ml), and 33 % (n = 3) had a history of diabetes; 44 % (n = 4) of patients had previously received immunosuppressive medication and 67 % (n = 6) received IVIG. The main indication for TPE was worsening of symptoms despite treatment with first-line therapy; 78 % of the patients (n = 7) had 5 TPE procedures; 78 % (n = 7) of patients demonstrated at least minimal clinical improvement and 56 % (n = 5) had a significant response. Most of the patients who demonstrated a significant response to treatment improved and their symptoms stabilized. Two patients (22 %) developed adverse events, including catheter-associated infection and transient hypotension. A total of 18 publications were found from the literature review, which resulted in a total of 26 patients diagnosed with SPS; 42 % (n = 11) of patients had a significant symptomatic improvement after TPE treatment, and 2 patients (8 %) developed adverse events. The authors concluded that TPE may benefit patients with SPS who are not responsive to first-line therapy, and it is well-tolerated. These preliminary findings need to be validated by well-designed studies.

Anti-Phospholipid Syndrome:

Kronbichler et al (2016) noted that extracorporeal treatments have been used since the 1970s in the management of systemic lupus erythematosus (SLE). A RCT comparing the effectiveness of standard of care (SOC) combined with PE against SOC alone in patients with lupus nephritis revealed no difference in terms of renal outcome. Subsequently, initial expectations have been dampened and further experience with PE is mainly limited to observational studies and single-case reports. Beneficial effects have been reported in patients with refractory disease course or in pregnancy with prior complications due to SLE and anti-phospholipid syndrome (APS). A more specific form of extracorporeal treatment, immunoadsorption (IAS), has emerged as a valuable option in the treatment of SLE. In line with the PE experience, IAS seems to have beneficial effects in patients with refractory disease, contraindications to standard immunosuppression or during pregnancy. The mechanism IAS relates to autoantibody removal but for PE removal of activated
complement components, coagulation factors, cytokines and micro-particles may also be relevant. Both treatment forms have good safety profiles although reactions to blood product replacement in PE and procedure related complications such as bleeding or catheter-related infections have occurred. The authors concluded that there is a need to more clearly define the clinical utility of PE and IAS in refractory lupus and APS subgroups.

Furthermore, an UpToDate review on “Therapeutic apheresis (plasma exchange or cytapheresis): Indications and technology” (Fridey and Kaplan, 2016) does not mention APS as an indication of therapeutic apheresis.

**Hypertriglyceridemia:**

Valdivielso and colleagues (2014) noted that severe hypertriglyceridemia (HTG) is a well-established and the most common cause of acute pancreatitis (AP) after alcohol and gall stone disease. It is alleged to account for up to 10% of all pancreatitis episodes. Studies suggested that in patients with triglyceride (TG) levels greater than 1,000 mg/dL (> 11.3 mmol/L), HTG-induced AP (HTGP-AP) occurs in approximately 15 to 20% of all subjects referred to Lipid Clinics. Until now, there is no clear evidence which patients with severe HTG will develop pancreatitis and which will not. Underlying pathophysiological concepts include hydrolysis of TG by pancreatic lipase and excessive formation of free fatty acids with inflammatory changes and capillary injury. Additionally hyper-viscosity and ischemia may play a decisive role. The clinical features of HTG-AP patients are supposed to be no different from patients with AP of other etiologies. Yet, there are well-conducted studies suggesting that HTG-AP is associated with a higher severity and complication rate. Therapeutic approaches in HTG-AP include dietary modifications, different anti-hyperlipidemic agents, insulin and/or heparin treatment. The beneficial use of plasmapheresis is repeatedly reported and suggested in many studies. Yet, due to the lack of randomized and controlled trials (RCTs), it is currently unknown if plasmapheresis may improve morbidity and mortality in the clinical setting of HTG-AP. Since there are no commonly accepted clinical guidelines in the management of HTG-AP, there
is a definite need for an international, multi-center approach to this important subject.

Scherer et al (2014) stated that HTG is a well-established but under-estimated cause of AP and recurrent AP. The clinical presentation of HTG-induced pancreatitis (HTG pancreatitis) is similar to other causes. Pancreatitis secondary to HTG is typically seen in the presence of 1 or more secondary factors (uncontrolled diabetes, alcoholism, medications, pregnancy) in a patient with an underlying common genetic abnormality of lipoprotein metabolism (familial combined hyperlipidemia or familial HTG). Less commonly, a patient with rare genetic abnormality (familial chylomiconemic syndrome) with or without an additional secondary factor is encountered. The risk of AP in patients with serum triglycerides greater than 1,000 and greater than 2,000 mg/dL is approximately 5 % and 10 % to 20 %, respectively. It is not clear whether HTG pancreatitis is more severe than when it is due to other causes. Clinical management of HTG pancreatitis is similar to that of other causes. Insulin infusion in diabetic patients with HTG can rapidly reduce TG levels. Use of apheresis is still experimental and better designed studies are needed to clarify its role in the management of HTG pancreatitis. Diet, lifestyle changes, and control of secondary factors are key to the treatment, and medications are useful adjuncts to the long-term management of TG levels. Control of TG levels to 500 mg/dL or less can effectively prevent recurrences of pancreatitis.

Click et al (2015) stated that mostly published as case reports or series, the role of apheresis in HTG-related AP remains unclear. These investigators performed a systematic review of available literature on this topic with specific focus on disease severity. A search of electronic databases (PubMed, EMBASE, Cochrane) and gray literature yielded 5,020 articles of which 74 met criteria for inclusion (301 unique patients). Relevant data were abstracted from full manuscripts and analyzed. Most patients were young (mean age of 37.9 ± 10.4 years) and male (71.5 %). About 2/3 (69.7 %) received apheresis within 48 hrs and most required only 1 or 2 sessions (84.4 %). Apheresis resulted in an average reduction of serum TG by 85.4 % (p < 0.001). There was high
variability in reporting the presence of and criteria to define severe AP (reported 221/301, 73.4 %; present 85/221, 38.5 %) or organ failure (reported 104/301, 34.6 %; present 52/104, 50.0 %). Improvement was reported in the majority of patients (reported 144/301, 47.8 %, present 136/144, 94.4 %) mainly by clinical symptoms or laboratory tests. Overall mortality was 7.1 % (21/294) which increased to 11.8 % (10/85) with severe AP and 19.2 % (10/52) with organ failure. The authors concluded that apheresis effectively reduced serum TG levels. However, due to uncontrolled data, reporting bias and lack of a comparison group, definitive conclusions on the efficacy of apheresis in reducing AP severity cannot be made. These researchers proposed which patients may be best suitable for apheresis, type of studies needed and outcome measures to be studied in order to provide empiric data on the role of apheresis in HTG-related AP.

An UpToDate review on “Hypertriglyceridemia-induced acute pancreatitis” (Gelrud and Whitcomb, 2016) states that “Apheresis -- Apheresis is a term describing the general process of passing blood through a medical device to separate any components, and returning the remaining components to the body. Plasmapheresis is the removal of up to 15 % of the plasma, filtration uses a membrane to remove components by size, and therapeutic plasma exchange (TPE) is the removal of plasma and replacement with a colloid solution (e.g., albumin or plasma). TPE is the treatment modality of choice for HTGP when apheresis is needed because filters become clogged by plasma triglycerides. We suggest treatment with apheresis, and specifically therapeutic plasma exchange (TPE) if the patient has a serum triglyceride level > 1,000 mg/dL plus lipase > 3 times the upper limit of normal and signs of hypocalcemia, lactic acidosis, or signs of worsening inflammation or organ dysfunction, and if there are no contraindications to apheresis (Grade 2C)."

IgG and IgA Paraproteinaemic Neuropathy:

In a Cochrane review, Stork et al (2015) examined the effects of any treatment for IgG or IgA paraproteinaemic peripheral neuropathy. On January 18, 2014 these investigators searched the Cochrane Neuromuscular Disease Group Trials Specialized
Register, CENTRAL, MEDLINE and EMBASE. They also checked bibliographies for controlled trials of treatments for IgG or IgA paraproteinaemic peripheral neuropathy. These researchers checked clinical trials registries for ongoing studies in November 2014. They considered for inclusion RCTs and quasi-RCTs using any treatment for IgG or IgA paraproteinaemic peripheral neuropathy. They excluded people with IgM paraproteins. They excluded people where the monoclonal gammopathy was considered secondary to an underlying disorder. They included participants of any age with a diagnosis of monoclonal gammopathy of uncertain significance with a paraprotein of the IgG or IgA class and a neuropathy. Included participants were not required to fulfill specific electrophysiological diagnostic criteria. These researchers used standard Cochrane methodology to select studies, extract data and analyze results. One trial author provided additional data and clarification. These researchers identified 1 RCT, with 18 participants, that fulfilled the predetermined inclusion criteria. The trial compared PE to sham PE in participants with IgG or IgA paraproteinaemic neuropathy over a 3-week follow-up period. They identified 4 other studies but these were not RCTs or quasi-RCTs. The included RCT did not report the pre-defined primary outcome measure, change in disability 6 months after randomization. The trial revealed a modest benefit of PE in the weakness component of the Neuropathy Disability Score (NDS, now the Neuropathy Impairment Score); the mean improvement with PE was 17 points (95% CI: 5.2 to 28.8 points) versus 1 point (95% CI: -7.7 to 9.7 points) in the sham PE group at 3 weeks' follow-up (mean difference (MD) 16.00; 95% CI: 1.37 to 30.63, low quality evidence). There was no statistically significant difference in the overall NDS (MD 18.00; 95% CI: -2.03 to 38.03, low quality evidence), vibration thresholds or neurophysiological indices. Adverse events were not reported. The trial was at low risk of bias overall, although limitations of trial size and duration reduce the quality of the evidence in support of its conclusions. The authors concluded that the evidence from RCTs for the treatment of IgG or IgA paraproteinaemic neuropathy is currently inadequate. More RCTs of treatments are needed. These should have adequate follow-up periods and contain larger numbers of participants, perhaps through multi-center collaboration,
considering the relative infrequency of this condition. Observational or open trial data provide limited support for the use of treatments such as PE, cyclophosphamide combined with prednisolone, intravenous immunoglobulin, and corticosteroids. These interventions showed potential therapeutic promise but the potential benefits must be weighed against adverse effects. Their optimal use and the long-term benefits need to be considered and validated with well-designed RCTs.

**Nephrogenic Systemic Fibrosis:**

Ridel et al (2017) stated that PE is a non-selective apheresis technique that can be performed by filtration or centrifugation allowing rapid purification of high molecular weight pathogens. An immunosuppressive treatment is generally associated to reduce the rebound effect of the purified substance. Substitution solutes such as human albumin and macromolecules are needed to compensate for plasma extraction. Compensation by viro-attenuated plasma is reserved solely for the treatment of thrombotic microangiopathies or when there is a risk of bleeding, because this product is very allergenic and expensive. The treatment goal for a PE session should be between 1 and 1.5 times the patient's plasma volume estimated at 40 ml/kg body weight. The anti-coagulation is best ensured by the citrate. Complications of PE are quite rare according to the French hemapheresis registry. The level of evidence of efficacy of PE in nephrology varies from one pathology to another. Main indications of PE in nephrology are Goodpasture syndrome, anti-neutrophil cytoplasmic antibody vasculitis when plasma creatinine is greater than 500 μmol/L, and thrombotic microangiopathies. During renal transplantation, PE may be proposed in the context of human leukocyte antigen (HLA) desensitization protocols or ABO-incompatible graft. After renal transplantation, PE is indicated as part of the treatment of acute humoral rejection or recurrent focal segmental glomerulosclerosis on the graft; PE are also proposed in the management of cryoglobulinemia or polyarteritis nodosa. Hemodialysis with membranes of very high permeability tends to replace PE for myeloma nephropathy. The authors stated that benefit from PE has not been formally demonstrated for the
treatment of severe lupus or APS. They noted that there is no indication of PE in the treatment of scleroderma or nephrogenic systemic fibrosis.

**Status Epilepticus:**

Zeiler et al (2016a) performed a scoping systematic review of the literature on the use of PP or PE for refractory status epilepticus (RSE) in adults. Articles from Medline, BIOSIS, Embase, Global Health, Healthstar, Scopus, Cochrane Library, the International Clinical Trials Registry Platform, clinicaltrials.gov (inception to May 2016), reference lists of relevant articles, and gray literature were searched. The strength of evidence was adjudicated using both the Oxford and GRADE methodology by 2 independent reviewers. A total of 22 original articles were identified; 27 adult patients were described in these articles, with a variety of autoimmune conditions leading to RSE. Seizure response with the application of PE therapy occurred in 14 of the 27 patients (51.9 %), with 1 (3.7 %) and 13 (48.1 %) displaying partial response (PR) and complete response (CR), respectively. Generalized RSE was the most likely seizure subtype to respond to PE therapy; 1 patient had recorded an adverse events (AE) related to PE therapy. The authors concluded that Oxford level 4, GRADE D evidence existed to suggest an uncertain response of adult autoimmune RSE to PE therapy. Thus, they stated that routine application of PE therapy for adult autoimmune RSE cannot be recommended at this time.

Zeiler et al (2016b) performed a scoping systematic review of the literature on the use of PP or PE for RSE in children. Articles from Medline, BIOSIS, Embase, Global Health, Healthstar, Scopus, Cochrane Library, the International Clinical Trials Registry Platform, clinicaltrials.gov (inception to May 2016), reference lists of relevant articles, and gray literature were searched. The strength of evidence was adjudicated using both the Oxford and GRADE methodology by 2 independent reviewers. A total of 22 original articles were identified, with 37 pediatric patients. The mean age of the patients was 8.3 years (median of 8.5, range of 0.6 to 17). Seizure response to PE therapy occurred in 9 of the 37 patients (24.3 %) included in the review, with 7 patients (18.9 %)
displaying resolution of seizures and 2 patients (5.4 %) displaying a partial reduction in seizure volume; 28 of the 37 patients (75.7 %) had no response to PE therapy; no AEs were recorded. The authors concluded that Oxford level 4, GRADE D evidence existed to suggest little to no benefit of PE in pediatric RSE. They stated that routine application of PE for pediatric RSE cannot be recommended at this time.

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**ICD-10 codes not covered for indications listed in the CPB:**

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<td>G20 - G21.9</td>
<td>Parkinson's disease</td>
</tr>
<tr>
<td>G25.82</td>
<td>Stiff-man syndrome</td>
</tr>
<tr>
<td>G30.0 - G30.9</td>
<td>Alzheimer's disease</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>G37.9</td>
<td>Other demyelinating diseases of central nervous system [anti-MAG neuropathy]</td>
</tr>
<tr>
<td>G50.0 - G60.0, G60.2 - G60.9, G61.1 - G61.89 - G65.2, G70.1, G70.9</td>
<td>Nerve disorders, nerve root and plexus disorders, mononeuritis, neuropathy, and myoneural disorders (except Refsum's disease, Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuritis, and myasthenia gravis) [neuropathy associated with immunoglobulin M gammopathy] [idiopathic progressive polyneuropathy] [anti-MAG neuropathy]</td>
</tr>
<tr>
<td>G72.9</td>
<td>Myopathy, unspecified [idiopathic]</td>
</tr>
<tr>
<td>H35.30 - H35.379</td>
<td>Degeneration of macula</td>
</tr>
<tr>
<td>H46.00 - H46.9</td>
<td>Optic neuritis</td>
</tr>
<tr>
<td>H91.20 - H91.23</td>
<td>Sudden idiopathic hearing loss</td>
</tr>
<tr>
<td>I02.9</td>
<td>Rheumatic chorea without heart involvement [Sydenham's chorea]</td>
</tr>
<tr>
<td>I20.0</td>
<td>Unstable angina [intermediate coronary syndrome]</td>
</tr>
<tr>
<td>I73.00 - I73.01</td>
<td>Raynaud's syndrome</td>
</tr>
<tr>
<td>J84.01</td>
<td>Alveolar proteinosis</td>
</tr>
<tr>
<td>K50.00 - K50.919</td>
<td>Crohns' disease [regional enteritis]</td>
</tr>
<tr>
<td>K85.00 - K85.92</td>
<td>Acute pancreatitis [related to hyperlipidemia]</td>
</tr>
<tr>
<td>L12.0</td>
<td>Bullous pemphigoid</td>
</tr>
<tr>
<td>L40.0 - L40.9</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>L50.8</td>
<td>Other urticaria [chronic urticaria]</td>
</tr>
<tr>
<td>N03.0</td>
<td>Chronic nephritic syndrome with diffuse mesangial proliferative glomerulonephritis [in kidney allograft]</td>
</tr>
<tr>
<td>R00.0</td>
<td>Tachycardia, unspecified [postural orthostatic tachycardia syndrome]</td>
</tr>
</tbody>
</table>
R53.82  Chronic fatigue, unspecified
R65.21  Sepsis with septic shock

*Leukapheresis*:

**CPT code covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>36511</td>
<td>Therapeutic apheresis: for white blood cells [for acute debulking only]</td>
</tr>
</tbody>
</table>

**ICD-10 codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C90.10</td>
<td>Plasma cell leukemia</td>
</tr>
<tr>
<td>C90.12</td>
<td></td>
</tr>
<tr>
<td>C91.0</td>
<td>Lymphoid, myeloid, monocytic, other specified, and unspecified leukemias</td>
</tr>
<tr>
<td>C95.92</td>
<td></td>
</tr>
</tbody>
</table>

*Therapeutic cytopheresis*:

**CPT code covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>36512</td>
<td>Therapeutic apheresis: for red blood cells</td>
</tr>
</tbody>
</table>

**ICD-10 codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>D57.00</td>
<td>Sickle-cell disorders</td>
</tr>
<tr>
<td>D57.819</td>
<td></td>
</tr>
</tbody>
</table>

**The above policy is based on the following references:**


45. Turner MS, Sutton D, Sauder DN. The use of plasmapheresis


118. Gelfand JA, Vannier E. Clinical manifestations, diagnosis, treatment, and prevention of babesiosis. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed December 2012.


122. Rosenson RS, Durrington P. HDL metabolism and approach
to the patient with abnormal HDL-cholesterol levels. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed December 2013.


133. Sibai BM. HELLP syndrome. UpToDate Inc., Waltham, MA.


143. Fridey JL, Kaplan AA. Therapeutic apheresis (plasma exchange or cytapheresis): Indications and technology. UpToDate Inc., Waltham, MA. Last reviewed January 2016.


Amendment to
Aetna Clinical Policy Bulletin Number: CPB 0285 -
Plasmapheresis/Plasma Exchange/Therapeutic Apheresis

There are no amendments for Medicaid.