Subject: Plasmapheresis for Renal and Non-renal Indications		**Original Effective Date:** 4/24/13
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PREFACE

This Medical Guidance is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusions or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the following website: http://www.cms.hhs.gov/center/coverage.asp.

FDA INDICATIONS

Plasmapheresis is a procedure that is not subject to FDA regulation. Therapeutic apheresis and related methods are performed by a device such as an automated blood cell separator or an affinity column, which uses whole blood, retains one or more of the components, and returns the remainder of the blood to the donor. The devices are classified as therapeutic blood cell and plasma automated separators. Some devices such as membrane apheresis devices, including filters, are classified as Class III devices and require a Premarket Approval (PMA) application before the device is marketed. The equipment that controls the blood pressure and flow rate during apheresis is considered substantially equivalent to Class II medical devices. [5]

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina medical coverage guidance (MCG) document and provide the directive for all Medicare members. The directives from this MCG document may be followed if there are no available NCD or LCD documents available and outlined below.

CMS does have a national coverage determination (NCD) for apheresis [1] as defined as an autologous procedure, where blood is taken from the patient, processed, and returned to the patient as part of a continuous procedure and covers for the following indications:

- Plasma exchange for acquired myasthenia gravis;
- Leukapheresis in the treatment of leukemia;
- Plasmapheresis in the treatment of primary macroglobulinemia (Waldenstrom);
- Treatment of hyperglobulinemias, including (but not limited to) multiple myelomas, cryoglobulinemia and hyperviscosity syndromes;

- Plasmapheresis or plasma exchange as a last resort treatment of thromobotic thrombocytopenic purpura (TTP);
- Plasmapheresis or plasma exchange in the last resort treatment of life threatening rheumatoid vasculitis;
- Plasma perfusion of charcoal filters for treatment of pruritis of cholestatic liver disease;
- Plasma exchange in the treatment of Goodpasture's Syndrome;
- Plasma exchange in the treatment of glomerulonephritis associated with antiglomerular basement membrane antibodies and advancing renal failure or pulmonary hemorrhage;
- Treatment of chronic relapsing polyneuropathy for patients with severe or life threatening symptoms who have failed to respond to conventional therapy;
- Treatment of life threatening scleroderma and polymyositis when the patient is unresponsive to conventional therapy;
- Treatment of Guillain-Barre Syndrome; and
- Treatment of last resort for life threatening systemic lupus erythematosus (SLE) when conventional therapy has failed to prevent clinical deterioration.

Apheresis is covered only when performed in a hospital setting (either inpatient or outpatient) or in a nonhospital setting, e.g., a physician directed clinic when the following conditions are met:

- A physician (or a number of physicians) is present to perform medical services and to respond to medical emergencies at all times during patient care hours;
- Each patient is under the care of a physician; and
- All nonphysician services are furnished under the direct, personal supervision of a physician.

INITIAL COVERAGE CRITERIA

1. Plasmapheresis may be authorized as medically necessary as a first line therapy for any of the following **renal** conditions:

   - ❑ Anti-glomerular basement membrane disease (Goodpasture's syndrome) [3 4]: [ONE]
     - o Dialysis independence
     - o Diffuse alveolar hemorrhage
   - ❑ ANCA-associated rapidly progressive glomerulonephritis (Granulomatosis with polyangiitis [Wegener's]) [3 4] : [ONE]
     - o Dialysis dependence
     - o Diffuse alveolar hemorrhage
   - ❑ Renal transplantation [3 4] : [ALL]
     - o Antibody mediated rejection

2. Plasmapheresis may be authorized as medically necessary for any of the following **non-renal** indications:

   - ❑ Acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome) when the following is present [3 4 9 18]: [ONE]
     - o Severe enough to impair independent walking; or
     - o Severe enough to require mechanical ventilation

- ❑ Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) [3 4 11]
- ❑ Cryoglobulinemia [3 4]: [ALL]
  - Severe and symptomatic
- ❑ Recurrent focal segmental glomerulosclerosis [3 4]
- ❑ Hyperviscosity syndrome in monoclonal gammopathies (e.g., Waldenström's macroglobulinemia, multiple myeloma) [3 4 17]: [ONE]
  - Treatment of symptoms; or
  - Prophylaxis for rituximab
- ❑ Myasthenia gravis [1 3 4 10 20]: [ONE]
  - Moderate-severe ; or
  - Pre-thymectomy
- ❑ Paraproteinemic polyneuropathy associated with [3 4 12:] [ONE]
  - immunoglobulin G (IgG); or
  - immunoglobulin A (IgA) or immunoglobulin M (IgM) monoclonal gammopathy of undetermined significance (e.g., MGUS)
- ❑ Thrombotic microangiopathy (TMA) drug induced secondary to [3 4] : [ONE]
  - ticlopidine; or
  - clopidogrel
- ❑ Thrombotic thrombocytopenic purpura (TTP) [3 4 23 26]
- ❑ Wilson's disease presenting as fulminant hepatic failure with hemolysis [3 4]

3. Plasmapheresis may be authorized as a medically necessary adjunctive secondary therapy for the following conditions when response to conventional therapy (e.g., corticosteroids or intravenous immunoglobulins [IVIG] has failed:

- ❑ ABO incompatible hematopoietic cell transplantation [3 4]: [ONE]
  - hematopoietic progenitor cell (HPC), marrow; or
  - hematopoietic progenitor cell (HPC), apheresis
- ❑ ABO incompatible solid organ transplantation [3 4] : [ONE]
  - Kidney; or
  - Heart (<40 months of age)
- ❑ Acute disseminated encephalomyelitis [3 4]
- ❑ Autoimmune hemolytic anemia [3 4] :
  - Cold agglutinin disease (life-threatening)
- ❑ Catastrophic antiphospholipid syndrome [3 4]
- ❑ Chronic focal encéphalites (Rasmussen's encéphalites) [3 4]
- ❑ Familial hypercholesterolemia [3 4] :
  - Homozygotes with small blood volume
- ❑ Hemolytic-uremic syndrome [3 4]
  - Atypical HUS due to complement factor gene mutations
- ❑ Lambert-Eaton myasthenic syndrome [3 4]
- ❑ Multiple sclerosis [3 4 8 22]

- Acute CNS inflammatory demyelinating disease unresponsive to steroids

- ❑ Myeloma cast nephropathy [21]
- ❑ Neuromyelitis optica (Devic's syndrome) [3 4]
- ❑ Mushroom poisoning [3 4]
- ❑ Phytanic acid storage disease (Refsum's disease) [3 4]
- ❑ Pure red cell aplasia [3 4]
- ❑ Red cell alloimmunization in pregnancy, before intrauterine transfusion availability [3 4]
- ❑ Renal transplantation [3 4]:
  - Desensitization, living donor, positive crossmatch due to donor specific HLA antibody
- ❑ Systemic lupus erythematosus [3 4]:
  - severe (eg, cerebritis, diffuse alveolar hemorrhage)

CONTINUATION OF THERAPY

N/A

COVERAGE EXCLUSIONS

Plasmapheresis is considered experimental and investigational [2 3 4 8] for all other indications because the medical literature does not support the clinical efficacy for the following conditions that include but are not limited to:

- ❑ ABO incompatible solid organ transplantation: Liver perioperative
- ❑ Acute liver failure
- ❑ ANCA-associated rapidly progressive glomerulonephritis (Wegener's Granulomatosis): Dialysis independence
- ❑ Aplastic anemia
- ❑ Autoimmune hemolytic anemia: Warm autoimmune hemolytic anemia
- ❑ Cardiac allograft rejection: Treatment of antibody mediated rejection
- ❑ Dilated cardiomyopathy: NYHA II-IV
- ❑ Hypertriglyceridemic pancreatitis [2]
- ❑ Immune complex rapidly progressive glomerulonephritis
- ❑ Multiple sclerosis: Chronic progressive or secondary progressive
- ❑ Nephrogenic systemic fibrosis
- ❑ Overdose, venoms, and poisoning: Envenomation, Monoclonal antibody with PML, Other compounds
- ❑ Paraneoplastic neurologic syndromes
- ❑ Paraproteinemic polyneuropathies: Multiple myeloma
- ❑ Pediatric postinfectious autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) [8]
- ❑ Pemphigus vulgaris
- ❑ Polyneuropathy associated with IgM MGUS
- ❑ Post-transfusion purpura

- ❑ Renal transplantation: High panel reactive antibody (PRA), cadaveric donor
- ❑ Rheumatoid arthritis
- ❑ Scleroderma (progressive systemic sclerosis)
- ❑ Sepsis with multiorgan failure
- ❑ Syndenham's chorea (severe exacerbation) [8]
- ❑ Thrombotic microangiopathy: drug-associated: Cyclosporine/tacrolimus
- ❑ Thrombotic microangiopathy: hematopoietic stem cell transplant-associated
- ❑ Thyroid storm

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

The terms plasmapheresis and therapeutic plasma exchange are often used interchangeably. However, in some cases, researchers may differentiate between plasma exchange and plasmapheresis. In plasma exchange, large volumes of patient plasma are exchanged with donor plasma or a plasma substitute. In plasmapheresis, the patient's plasma is separated from the cellular components of the blood. Following fractionation, the cellular components are returned to the patient.

Plasma exchange and plasmapheresis are conducted in outpatient settings, including blood banks, dialysis centers, hospitals, and physicians' offices. Blood is withdrawn from patient or donor, generally from the antecubital vein. Blood cell separators are connected to the patient or donor via flexible tubing. An anticoagulant, typically sodium citrate, is added to the collected venous blood. The blood is then pumped into the extracorporeal circuit tubing leading to a spinning centrifugal container. The blood is fractionated, or separated, according to the density of the blood components. Fractionation causes the red blood cells to sink to the bottom of the container, the plasma stays on top, and the white blood cells and platelet are suspended between the red blood cells and plasma. The plasma may be further fractionated to separate plasma proteins such as albumin, immunoglobulin, and clotting factors. The affected plasma is gathered for disposal.

Replacement fluids are automatically infused into the patient to maintain intravascular volume and pressure homeostasis. Common replacement fluids include crystalloids, allogeneic fresh frozen plasma, and colloids or plasma protein fractions. The crystalloid is typically a mixture of an anticoagulant and normal saline. The colloid, usually 5% to 25% albumin, provides approximately 60% to 80% of the total fluid infused. The choice and exact combination of replacement solutions for therapeutic plasmapheresis are prescribed by a physician based on the patient's physical condition and underlying disease, and the planned frequency of the procedure. However, no standard criteria exist regarding the optimal treatment schedule for plasma exchanges and the type or volume of replacement fluids.

GENERAL INFORMATION

Summary of Medical Evidence

Renal Indications:

Baweja and associates (2011) performed a systematic review of recent and past evidence and the current indications for treatment in renal disease. Recently, results from several randomized controlled trials, meta-analyses, and prospective studies have shown plasmapheresis may be of benefit in various renal diseases, and have provided insights into more rational use of this therapy. A multicenter trial by the European Vasculitis Study Group has shown it is the preferred additional form of therapy for patients with anti-neutrophil cytoplasmic antibody-associated glomerulonephritis and severe renal failure. A recent study conducted at Mayo Clinic also found it effective at reversing renal failure from myeloma-related cast nephropathy if serum free light chain levels were reduced by at least 50%. In addition, a Cochrane review has analyzed the available evidence for its use in thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. [24]

Walsh and associates (2011) performed a systematic review and meta-analysis of randomized controlled trials of plasma exchange in adults with idiopathic renal vasculitis or rapidly progressive glomerulonephritis. Randomized controlled trials that compared standard care with standard care plus adjuvant plasma exchange in adult patients with either renal vasculitis or idiopathic rapidly progressive glomerulonephritis were reviewed. 9 trials including 387 patients were found. In a fixed-effects model, the pooled RR for end-stage renal disease or death was 0.80 for patients treated with adjunctive plasma exchange compared with standard care alone (95% CI, 0.65-0.99; P = 0.04). No significant heterogeneity was detected (P = 0.5; I(2) = 0%). The effect of plasma exchange did not differ significantly across the range of baseline serum creatinine values (P = 0.7) or number of plasma exchange treatments (P = 0.8). The RR for end-stage renal disease was 0.64 (95% CI, 0.47-0.88; P = 0.006), whereas the RR for death alone was 1.01 (95% CI, 0.71-1.4; P = 0.9). The reviewers concluded that plasma exchange may decrease the composite end point of end-stage renal disease or death in patients with renal vasculitis. [32]

Cui and colleagues (2011) conducted a retrospective survey of 221 consecutive patients seen from 1998 to 2008 in one hospital and reported on the patient and renal survival and the risk factors affecting the outcomes. The effects of 3 different treatment regimens were compared: 1) combination therapy of plasmapheresis and immunosuppression, 2) steroids and cytotoxic agents, and 3) steroids alone. The patient and renal survival rates were 72.7% and 25.0%, respectively, at 1 year after disease presentation. The serum level of anti-GBM antibodies (increased by 20 U/mL; hazard ratio [HR], 1.16; p = 0.009) and the presentation of positive antineutrophil cytoplasmic antibodies (ANCA) (HR, 2.18; p = 0.028) were independent predictors for patient death. The serum creatinine at presentation (doubling from 1.5 mg/dL; HR, 2.07; p < 0.001) was an independent predictor for renal failure. The combination therapy of plasmapheresis plus corticosteroids and cyclophosphamide had an overall beneficial effect on both patient survival (HR for patient mortality, 0.31; p = 0.001) and renal survival (HR for renal failure, 0.60; p = 0.032), particularly patient survival for those with Goodpasture syndrome (HR for patient mortality, 0.29; p = 0.004) and renal survival for those with anti-GBM nephritis with initial serum creatinine over 6.8 mg/dL (HR for renal failure, 0.52; p = 0.014). The treatment with corticosteroids plus cyclophosphamide was found not to improve the renal outcome of disease (p = 0.73). In conclusion, the combination therapy was preferred for patients with anti-GBM disease, especially those with pulmonary hemorrhage or severe renal damage. Early diagnosis was crucial to improving outcomes. [34]

Walters and associates (2010) conducted systematic review to determine the benefits and harms of any intervention for the treatment of renal vasculitis in adults. Statistical analyses were performed using a random effects model and results expressed as risk ratio with 95% confidence intervals for dichotomous outcomes or mean difference for continuous outcomes. Twenty two studies (1674 patients) were included. Plasma exchange as adjunctive therapy significantly reduces the risk of end-stage kidney disease at 12 months (five studies: RR 0.47, CI 0.30 to 0.75). Four studies compared the use of pulse and continuous administration of cyclophosphamide. Remission rates were equivalent but pulse treatment causes an increased risk of relapse (4 studies: RR 1.79, CI 1.11 to 2.87) compared with continuous cyclophosphamide. Azathioprine has equivalent efficacy as a maintenance agent to cyclophosphamide with fewer episodes of leukopenia. Mycophenolate mofetil may be equivalent to cyclophosphamide as an induction agent but resulted in a higher relapse rate when tested against Azathioprine in remission maintenance. Rituximab is an effective remission induction agent. Methotrexate or Leflunomide are potential choices in remission maintenance therapy. Oral co-trimoxazole did not reduce relapses significantly in Wegener's granulomatosis. The authors concluded that plasma exchange is effective in patients with severe ARF secondary to vasculitis. Pulse cyclophosphamide results in an increased risk of relapse when compared to continuous oral use but a reduced total dose. Whilst cyclophosphamide is standard induction treatment, rituximab and mycophenolate mofetil are also effective. Azathioprine, methotrexate and leflunomide are effective as maintenance therapy. Further studies are required to more clearly delineate the appropriate place of newer agents within an evidence-based therapeutic strategy. [33]

Gupta and colleagues performed a systematic review (2010) of three randomized controlled trials (RCTs) and multiple observational trials to evaluate the potential role of plasmapheresis in the management of multiple myeloma complicated by acute renal failure. This systematic review presents the results of these trials regarding survival benefits, recovery from dialysis, and improvement in renal function. A comprehensive search revealed 56 articles. Of these, only 8 articles met inclusion criteria (3 RCTs, 1 correction of results, and 4 observational trials). Two of the 3 RCTs showed no difference in survival benefit. Two of the 3 RCTs showed a greater percentage of patients stopping dialysis in the intervention group; however, these results were not reproduced in the largest trial. All the studies showed an improvement in renal function for patients receiving plasmapheresis; however, only 2 RCTs and 1 retrospective study showed a statistically significant improvement in renal function among patients who received plasmapheresis in comparison with a control group. The authors concluded that this systematic review does not suggest a benefit of plasmapheresis independent of chemotherapy for multiple myeloma patients with acute renal failure in terms of overall survival, recovery from dialysis, or improvement in renal function. [26]

Tobian and associates (2008) performed a systematic review to evaluate the role of therapeutic plasma exchange (TPE) to remove ABO antibodies and permit ABO-incompatible (ABO-I) kidney transplants. The TPE treatment plan is based on ABO titers with the goal of a titer of 16 or less at the anti-human globulin (AHG) phase before surgery. Pretransplant therapy consists of every-other-day TPE followed immediately by cytomegalovirus hyperimmune globulin. ABO antibody titers are closely monitored before and after

transplantation. After transplantation, TPE therapy is performed for all patients to prevent rebound of anti-A and anti-B titers until tolerance or accommodation occurs. TPE is discontinued and reinstituted based on the clinical criteria of creatinine levels, biopsy results, and ABO titer. Fifty-three ABO-I kidney transplants have been completed with no episodes of hyperacute antibody-mediated rejection (AMR) and only three episodes of AMR. One-year death-censored graft survival is 100 percent and patient survival is 97.6 percent. The review concluded that while randomized clinical trials are needed to evaluate the optimal method and protocol to remove ABO antibodies, the current literature and our results indicate a critical role for TPE in ABO-I renal transplantation. [28]

Non-renal Indications:

Huang and colleagues (2012) performed a prospective randomized controlled study to compare the therapeutic effect of molecular adsorbent re-circulating system (MARS) treatment (MARS group, n=60) with that of plasma exchange (PE) combined with MARS treatment (PE+MARS group, n=60) in patients with liver failure complicated with hepatic encephalopathy. The serum total bilirubin and blood ammonia levels were significantly decreased compared with pretreatment levels after 3 days of both the MARS treatment ($p=0.0001$, $p<0.001$) and PE+MARS treatment (both $p<0.0001$) and the Glasgow coma scale score was significantly increased (both $p<0.0001$). The 30-day mortality rate was 10.0% (6/60) in the MARS group and 11.7% (7/60) in the PE + MARS group. The per capita cost of treatment was significantly lower in the PE + MARS group than in the MARS group ($p=0.0003$). The authors concluded that both MARS and PE + MARS therapy can safely and effectively be used to treat liver failure complicated with hepatic encephalopathy, but PE + MARS therapy reduces serum total bilirubin level more effectively and is more cost-effective. [30]

Weiss and associates (2012) conducted an 8-year retrospective cohort study of children (≤18 years) with an international classification of diseases-9-clinical modification (ICD-9-CM) discharge diagnosis indicating an ASFA Category I or II condition, or a procedure code indicating receipt of TPE during hospitalization. Results: TPE was performed during 4,190 hospitalizations of 3,449 patients, of whom 310 (9.0%) and 77 (2.2%) had a primary discharge diagnosis of an ASFA Category I or II condition, respectively. Rates of TPE use for Category I conditions were highest for children with thrombotic thrombocytopenic purpura (TTP), Goodpasture's syndrome, and myasthenia gravis. TPE use in children's hospitals significantly increased from 2003 to 2010, but TPE was performed during only 13.4 and 9.3% of hospitalizations for ASFA Category I and II conditions, respectively. There was significant between-hospital variation in the use of TPE for Category I conditions as a group and individual Category I conditions including TTP. The authors found low levels of TPE use across hospitals for key indications, including TTP, a condition for which TPE is considered a first-line and life-saving procedure. The variation identified may contribute to varying clinical outcomes between hospitals, warrants further investigation, and represents an important opportunity to improve quality of care. [35]

El-Bayoumi and colleagues (2011) preformed prospective randomized study to compare the outcome of intravenous immunoglobulin (IVIG) and plasma exchange (PE) treatment in children with Guillain Barré

syndrome (GBS) requiring mechanical ventilation. Forty-one children with GBS requiring endotracheal mechanical ventilation (MV) within 14 days from disease onset were included. The ages of the children ranged from 49 to 143 months. Randomly, 20 children received a five-day course of IVIG (0.4 g/kg/day) and 21 children received a five-day course of one volume PE daily. Lumbar puncture (LP) was performed in 36 patients (18 in each group). Both groups had comparable age (p = 0.764), weight (p = 0.764), duration of illness prior to MV (p = 0.854), preceding diarrhea (p = 0.751), cranial nerve involvement (p = 0.756), muscle power using Medical Research Council (MRC) sum score (p = 0.266) and cerebrospinal fluid (CSF) protein (p = 0.606).Children in the PE group had a shorter period of MV (median 11 days, IQR 11.0 to 13.0) compared to IVIG group (median 13 days, IQR 11.3 to 14.5) with p = 0.037.Those in the PE group had a tendency for a shorter Pediatric Intensive Care Unit (PICU) stay (p = 0.094).A total of 20/21 (95.2%) and 18/20 (90%) children in the PE and IVIG groups respectively could walk unaided within four weeks after PICU discharge (p = 0.606).There was a negative correlation between CSF protein and duration of mechanical ventilation in the PE group (p = 0.037), but not in the IVIG group (p = 0.132). The authors concluded that in children with GBS requiring MV, PE is superior to IVIG regarding the duration of MV but not PICU stay or the short term neurological outcome. The negative correlation between CSF protein values and duration of MV in PE group requires further evaluation of its clinical usefulness. [31]

Martin and associates (2011) conducted a systematic review to evaluate the safety and efficacy of interventions for pemphigus vulgaris and pemphigus foliaceus. Randomized controlled trials including participants with the diagnosis of pemphigus vulgaris or pemphigus foliaceus confirmed with clinical, histopathological, and immunofluorescence criteria were selected. All interventions were considered. Primary outcomes studied were remission and mortality. Secondary outcomes included disease control, relapse, pemphigus severity score, time to disease control, cumulative glucocorticoid dose, serum antibody titers, adverse events, and quality of life. Eleven studies with a total of 404 participants were identified. Interventions assessed included prednisolone dose regimen, pulsed dexamethasone, azathioprine, cyclophosphamide, cyclosporine, dapsone, mycophenolate, plasma exchange, topical epidermal growth factor, and traditional Chinese medicine. We found some interventions to be superior for certain outcomes, although we were unable to conclude which treatments are superior overall. The authors concluded that there is inadequate evidence available at present to ascertain the optimal therapy for pemphigus vulgaris and pemphigus foliaceus. Further randomized controlled trials are required. [37]

Liu and colleagues (2010) performed a randomized controlled trial to investigate the effects of double-filtration plasmapheresis (DFPP), immunoadsorption (IA) and intravenous immunoglobulin (IVIg) in the treatment of late-onset myasthenia gravis (MG). A total of 40 late-onset MG patients were randomly divided into three groups: 15 patients were treated with DFPP; 10 patients were treated with IA; and 15 patients received IVIg. The titers of titin antibodies (Titin-ab), acetylcholine receptor antibodies (AChR-ab), presynaptic membrane antibody (Prsm-ab) were detected before and after the treatment, and the quantitative MG score (QMG score) was assessed by blinded examiners before and immediately after the entire course of treatment. The clinical efficacy, duration of respiratory support, hospital stay, and the correlation between the three antibodies and the QMG score were also analyzed. Compared to pre-treatment, the values of Titin-ab, AChR-ab, and PrsmR-ab

were all dramatically decreased (P < 0.05); meanwhile the value of Titin-ab in the DFPP and IA groups decreased much more than in the IVIg group (P < 0.01); however, no statistical difference was found between the DFPP and IA groups (P > 0.05). Although the QMG score significantly improved in all three groups, it decreased much more in both the DFPP and IA groups than that in the IVIg group (P < 0.01). Symptoms were also effectively ameliorated by all treatments, but the clinical efficacy of the DFPP and IA groups was higher than the IVIg group (P < 0.05), as was the remission time (P < 0.01), the duration of hospital stay (P < 0.05), and the number of respiratory supports required (P < 0.05). Using Pearson's correlation, the decrease of Titin-ab showed a longitudinal correlation with the decrease of QMG score (r = 0.6107, P < 0.01). The authors concluded that both DFPP and IA showed better short-term clinical effectiveness than immunoglobulin transfusion, rapidly and effectively clearing the pathogenic antibodies in late-onset MG patients, especially for Titin-ab. [29]

Zechmeister and associates (2009) performed a systematic review to evaluate apheresis in patients with familial hypercholesterolemia who are resistant to drug therapy and whether the various apheresis techniques available result in relevant improvement of clinical endpoints (cardiovascular morbidity and mortality, quality of life). Evidence from the ten studies included weakly indicates an improvement in angina symptoms and reduced mortality. However, due to limited study quality, no reliable answers are possible concerning the question whether LDL apheresis results in reduced cardiovascular morbidity/mortality or improved quality of life. The review concluded that the available evidence indicates a possible net benefit of LDL apheresis. However, since the quality of the evidence is very low, treatment should be strictly restricted to patients with severe familial hypercholesterolemia who are resistant to standard care. [27]

Bonnan and colleagues (2009) retrospectively studied the outcome of plasma exchange (PE) treated versus steroid-only treated spinal attacks in relapsing neuromyelitis optica (NMO) and extensive transverse myelitis (ETM). Ninety-six severe spinal attacks in 43 Afro-Caribbean patients were included in the study. PE was given as an add-on therapy in 29 attacks. Expanded disability status score (EDSS) was obtained before attack, during the acute and residual stage. We defined the DeltaEDSS as the rise from basal to residual EDSS. The DeltaEDSS was found to be lower in the PE-treated group (1.2 +/- 1.6 vs 2.6 +/- 2.3; P < 0.01). A low basal impairment is associated with a better outcome. Improvement was obtained in both NMO-IgG negative and positive NMO attacks. Minor adverse events manifested in seven PE sessions (24%). The authors concluded PE appears to be a safe add-on therapy that may be employed early in severe spinal attacks in the NMO spectrum disorders in order to maximize improvement rate. PE efficiency is independent of NMO-IgG positivity. [15]

Kaynar and colleagues (2008) performed a retrospective review of the medical records of 57 neurological patients consecutively treated with therapeutic plasma exchange (TPE). TPE indications in neurological diseases included Guillain-Barrè Syndrome (GBS) (n=41), myasthenia gravis (MG) (n=11), acute disseminated encephalomyelitis (ADEM) (n=3), chronic inflammatory demyelinating polyneuropathy (CIDP) (n=1) and multiple sclerosis (MS) (n=1). Patient median age was 49; there was a predominance of males. Twenty-two

patients had a history of other therapy including intravenous immunoglobulin (IVIG), steroid, azothioprin, and pridostigmine prior to TPE. Another 35 patients had not received any treatment prior to TPE. All patients were classified according to the Hughes functional grading scores pre- and first day post-TPE for early clinical evaluation of patients. The TPE was carried out 1-1.5 times at the predicted plasma volume every other day. Two hundred and ninety-four procedures were performed on 57 patients. The median number of TPE sessions per patient was five, and the median processed plasma volume was 3075mL for each cycle. Although the pre-TPE median Hughes score of all patients was 4, it had decreased to grade 1 after TPE. While the pre-TPE median Hughes score for GBS and MG patients was 4, post-TPE scores were decreased to grade 1. Additionally, there was a statistically significant difference between post-TPE Hughes score for GBS patients with TPE as front line therapy and patients receiving IVIG as front line therapy (1 vs. 3.5; p=0.034). Although there was no post-TPE improvement in Hughes scores in patients with ADEM and CIDP, patients with MS had an improved Hughes score from 4 to 1. Mild and manageable complications such as hypotension and hypocalcemia were also observed. The authors concluded TPE may be preferable for controlling symptoms of neuroimmunological disorders in early stage of the disease, especially with GBS. [16]

Ruma and associates (2007) conducted a retrospective multicenter case series. Patients with a history of early second-trimester fetal loss secondary to severe maternal red cell alloimmunization or patients with markedly elevated maternal antired cell titers felt to be consistent with poor fetal outcome were offered treatment. Therapy consisted of serial plasmapheresis followed by weekly infusions of intravenous immune globulin (IVIG). Maternal titers were measured before and after plasmapheresis. Pregnant patients with either a history of a previous perinatal loss (n = 7) or markedly elevated maternal antibody titers (n = 2) were treated with combined plasmapheresis and IVIG. All 9 fetuses subsequently required intrauterine transfusions (median 4; range 3-8). All infants survived with a mean gestational age at delivery of 34 weeks (range 26-38 weeks). Maternal antired cell titers were significantly reduced after plasmapheresis ($P < .01$) and remained decreased during IVIG therapy. Serial peak middle cerebral artery velocities remained below the threshold for moderate to severe fetal anemia during therapy. The authors concluded that combined immunomodulation with plasmapheresis and IVIG represents a successful approach to the treatment of severe maternal red cell alloimmunization. [36]

Hayes, Cochrane, UpToDate, MD Consult etc.

The Hayes Technology reports have been archived in 2006-2007 for the topics of plasmapheresis for renal and non-renal indications. There is a Hayes Technology brief report (November 2011) on plasmapheresis for Hypertriglyceridemia (HTG)-Induced Pancreatitis [2]. This report indicates that there is limited evidence on the efficacy and safety of plasmapheresis for HTG-induced pancreatitis. The evidence consists of 2 prospective and 4 retrospective studies with a total study population of fewer than 200 patients that reported reduction in serum triglyceride levels of 61% to 83% following PE as a treatment for HTG-induced pancreatitis. There are no studies comparing anticoagulation methods (heparin versus citrate), replacement fluids (albumin versus fresh frozen plasma), or time from diagnosis to start of PE. The quality of the evidence was very low due to poor study design, small sample size, and lack of a control group. Larger, controlled, long-term clinical studies are

needed to demonstrate clinical efficacy and assure safety of the procedure. Future research also needs to address the various technical aspects of the procedure to define evidence-based standard PE schedules for these severely ill patients.

There are Cochrane reports available on plasma exchange for various diseases:

Guillain-Barré syndrome: [9]

A Cochrane review was published (2012) to assess the effects of plasma exchange for treating Guillain-Barré syndrome. Selection criteria included randomised and quasi-randomised trials of plasma exchange versus sham exchange or supportive treatment. In one trial with 220 severely affected participants, the median time to recover walking with aid was significantly faster; with plasma exchange (30 days) than without (44 days). In another trial with 91 mildly affected participants, the median time to onset of motor recovery was significantly shorter with plasma exchange (six days) than without (10 days). After four weeks, combined data from three trials accounting for a total of 349 patients showed that plasma exchanged significantly increased the proportion of patients who recovered the ability to walk with assistance (risk ratio (RR) 1.60, 95% confidence interval (CI) 1.19 to 2.15). In five trials with 623 participants in total, the RR of being improved by one or more grades after four weeks was 1.64 (95% CI 1.37 to 1.96) in favor of plasma exchange. Participants treated with plasma exchange also fared significantly better in time to recover walking without aid (three trials with 349 participants, RR 1.72 (95% CI 1.06 to 2.79) and requirement for artificial ventilation (five trials with 623 participants, RR 0.53 (95% CI 0.39 to 0.74). There were significantly more participants with relapses by the end of follow-up in the plasma exchange than the control group (6 trials with 649 participants, RR 2.89 (95% CI 1.05 to 7.93). Despite this, at one year the likelihood of full muscle strength recovery was significantly greater with plasma exchange than without (five trials with 404 participants, RR 1.24 (95% CI 1.07 to 1.45) and the likelihood of severe motor sequelae was significantly less (six trials with 649 patients, RR 0.65 (95% CI 0.44 to 0.96). There was no significant difference in deaths (six trials with 649 participants, RR 0.86 (95% CI 0.45 to 1.65) or participants with adverse events (three trials with 556 participants), except fewer arrhythmias in plasma exchange treated participants (RR 0.75 (95% CI 0.56 to 1.00). The review concluded that moderate-quality evidence shows significantly more improvement with plasma exchange than supportive care alone in adults with Guillain-Barré syndrome without a significant increase in serious adverse events. There was a small but significant increase in the risk of relapse during the first six to 12 months after onset in people treated with plasma exchange compared with those that were not treated. Despite this, after one year, full recovery was significantly more likely and severe residual weakness less likely with plasma exchange.

Haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura:[25]

A Cochrane review was published (2011) to evaluate the benefits and harms of different interventions for HUS and TTP separately, in patients of all ages. Selection criteria included randomised controlled trials (RCTs) evaluating any interventions for HUS or TTP in patients of all ages. For TTP, we found six RCTs (331 participants) evaluating PE with FFP as the control. Interventions tested included antiplatelet therapy (APT) plus PE with FFP, FFP transfusion and PE with cryosupernatant plasma (CSP). Two studies compared plasma

infusion (PI) to PE with FFP and showed a significant increase in failure of remission at two weeks (RR 1.48, 95% 1.12 to 1.96) and all-cause mortality (RR 1.91, 95% 1.09 to 3.33) in the PI group. Seven RCTs were undertaken in children with HUS. None of the assessed interventions used (FFP transfusion, heparin with or without urokinase or dipyridamole, shiga toxin binding protein and steroids) were superior to supportive therapy alone, for all-cause mortality, neurological/extrarenal events, renal biopsy changes, proteinuria or hypertension at the last follow-up visit. Bleeding was significantly higher in those receiving anticoagulation therapy compared to supportive therapy alone (RR 25.89, 95% CI 3.67 to 182.83). The authors concluded that PE with FFP 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 diarrhoeal form of the disease. There were no RCTs evaluating the effectiveness of any interventions on patients with atypical HUS who have a more chronic and relapsing course.

Myasthenia gravis: [10]

A Cochrane review was published (2011) to examine the efficacy of plasma exchange in the short- and long-term treatment of myasthenia gravis. Selection criteria included all randomised controlled trials (RCTs) or quasi-RCTs including all patients with generalised myasthenia gravis. Treatment trials of plasma exchange alone or combined with steroids or immunosuppressive drugs were considered. The primary outcome measures were :(1) for exacerbation: change in a specific muscle score;(2) for chronic myasthenia gravis: change in a functional scale. Four RCTs with 148 participants in total were identified. In the first one, of 14 participants with moderate or severe myasthenia gravis, improvement after one month was not significantly greater for participants treated with plasma exchange and prednisone than for those treated with prednisone alone. A randomised controlled cross-over trial of 12 participants with moderate to severe myasthenia gravis found no statistically significant difference in the efficacy of plasma exchange or intravenous immunoglobulins after four weeks. A trial including 87 participants with myasthenia gravis exacerbation found no statistically significant difference between plasma exchange and immunoglobulin after two weeks. The fourth RCT, with 35 participants, showed a statistically significant difference in favour of plasma exchange before thymectomy. However these trials, except the third, are at high risk of bias and have a weak statistical power. The review concluded that there are no adequate RCTs that have been performed to determine whether plasma exchange improves the short- or long-term outcome for chronic myasthenia gravis or myasthenia gravis exacerbation. However, many studies with case series report short-term benefit from plasma exchange in myasthenia gravis, especially in myasthenic crisis. In severe exacerbations of myasthenia gravis one RCT did not show a significant difference between plasma exchange and intravenous immunoglobulin. Further research is needed to compare plasma exchange with alternative short-term treatments for myasthenic crisis or before thymectomy and to determine the value of long-term plasma exchange for treating myasthenia gravis.

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): [11]

A Cochrane review published in 2012 evaluated the efficacy of plasma exchange in CIDP. Selection criteria included randomised controlled trials (RCTs) or quasi-RCTs in participants of any age comparing plasma

exchange with sham treatment or no treatment. Primary outcome measure: one cross-over trial including 18 participants showed two (95% confidence interval (CI) 0.8 to 3.0) points more improvement after four weeks on an 11-point disability scale with plasma exchange (10 exchanges over four weeks) than with sham exchange. Rapid deterioration after plasma exchange occurred in eight of 12 who had improved. Secondary outcome measures: when the results of this trial and another with 29 participants treated in a parallel group design trial were combined, there were 31 points (95% CI 16 to 45, maximum score 280) more improvement in an impairment scale after plasma exchange (six exchanges over three weeks) than after sham exchange. There were significant improvements in both trials in an electrophysiological measure, the proximally evoked compound muscle action potential, after three or four weeks. Non-randomised evidence indicates that plasma exchange induces adverse events in 3% to 17% of procedures. These are sometimes serious. A trial showing no significant difference in the benefit between plasma exchange and intravenous immunoglobulin has been included in the Cochrane review of intravenous immunoglobulin for this condition. The review concluded that moderate to high quality evidence from two small trials showed that plasma exchange provides significant short-term improvement in disability, clinical impairment and motor nerve conduction velocity in CIDP but rapid deterioration may occur afterwards. Adverse events related to difficulty with venous access, use of citrate and haemodynamic changes are not uncommon. More research is needed to identify agents which will prolong the beneficial action of plasma exchange.

Treatment for IgG and IgA paraproteinaemic neuropathy: [12]

A Cochrane review published in 2006 examined the efficacy of any treatment for IgG or IgA paraproteinaemic peripheral neuropathy. Randomised and quasi-randomised controlled trials using any treatment for IgG or IgA paraproteinaemic peripheral neuropathy were included. People with IgM paraproteins were excluded. We excluded participants where the monoclonal gammopathy was considered secondary to an underlying disorder. We 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. Only one randomised controlled trial with 18 participants was identified that fulfilled the predetermined inclusion criteria. Four other trials were identified but these were not randomised controlled trials. The included trial revealed a modest short-term benefit of plasma exchange in IgG or IgA paraproteinaemic neuropathy, over a short follow-up period, when compared to sham plasma exchange. The review concluded that the evidence from randomised controlled trials for the treatment of IgG or IgA paraproteinaemic neuropathy is currently inadequate. More randomised controlled trials of treatments are required. These should have adequate follow-up periods and contain larger numbers of participants, perhaps through multicentre collaboration, considering the relative infrequency of this condition. Observational or open trial data provide limited support for the use of treatments such as plasma exchange, cyclophosphamide combined with prednisolone, intravenous immunoglobulin and corticosteroids. These show 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 randomised controlled trials.

Renal vasculitis: [13]

A Cochrane review was published in 2008 to determine the benefits and harms of any intervention for the treatment of renal vasculitis in adults. Selection criteria included randomised controlled trials investigating any intervention for the treatment of in adults. Thirteen studies (702 patients) were included. Plasma exchange as adjunctive therapy significantly reduces the risk of end-stage kidney disease (ESKD) at three months (one study: RR 0.45, 95% CI 0.24 to 0.84) and 12 months (five studies: RR 0.47, CI 0.24 to 0.86). Three studies compared the use of pulse and continuous administration of cyclophosphamide (CPA). Overall analysis showed a significant increase in remission with pulse CPA (2 studies: RR 1.17; 95%CI 1.02-1.35) and fewer relapses with continuous CPA. A single study addressed the use of azathioprine (AZA) after three months of CPA therapy, showing no difference in outcome except for significantly less leukopenia in patients on AZA. One study into the use of antibiotics to prevent relapse in Wegener's granulomatosis failed to show a significant effect. The review concluded that plasma exchange is effective in patients with severe ARF secondary to vasculitis. On current data, the use of pulse CPA results in an increased risk of relapse when compared to continuous use but a reduced total dose. The use of cotrimoxazole is likely to be beneficial to prevent relapse of vasculitis. AZA is effective as maintenance therapy once remission has been achieved.

Bullous pemphigoid (BP):[14]

A Cochrane review published in 2010 assessed treatments for bullous pemphigoid. Selection criteria included randomised controlled trials of treatments for participants with immunofluorescence-confirmed bullous pemphigoid. 10 randomised controlled trials (with a total of 1049 participants) of moderate to high risk of bias were included. All studies involved different comparisons, none had a placebo group. In 1 trial plasma exchange 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 (one trial each), for azathioprine plus prednisone compared with prednisone alone (one trial), for prednisolone plus azathioprine compared with prednisolone plus plasma exchange (one trial), for prednisolone plus mycophenolate mofetil or plus azathioprine (one trial), for tetracycline plus nicotinamide compared with prednisolone (one trial). Chinese traditional medicine plus prednisone was not effective in one 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% 0.97 to 1.03) in one 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 review 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 plasma exchange, azathioprine or mycophenolate mofetil to corticosteroids, and combination treatment with tetracycline and nicotinamide needs further investigation.

UpToDate:

1. There is a report on indications for therapeutic plasma exchange (TPE) (2012) [3] that indicates most TPE procedures are performed for neurologic, immunologic, or hematologic diseases and summarizes the general categories of TPE indications based upon an extensive review of the literature:
   - Category I — Disorders for which apheresis is accepted as first-line therapy, either as primary stand-alone treatment or in conjunction with other modes of treatment. Examples: Plasma exchange for Guillain-Barré syndrome as first-line stand alone therapy; plasma exchange for hyperviscosity in monoclonal gammopathies; plasma exchange for thrombotic thrombocytopenic purpura and red blood cell exchange in sickle cell disease and acute stroke.
   - Category II — Disorders for which apheresis is accepted as second-line therapy, either as a stand-alone treatment or in conjunction with other modes of treatment. Examples: plasma exchange as stand-alone secondary treatment for acute disseminated encephalomyelitis after high-dose intravenous corticosteroid failure; plasma exchange for life-threatening cold agglutinin disease and red blood cell exchange for acute chest syndrome in sickle cell disease.
   - Category III — Disorders for which the optimum role of apheresis therapy is not established. Decision making should be individualized. Examples: Extracorporeal photopheresis for nephrogenic systemic fibrosis; plasma exchange in patients with sepsis and multiorgan failure; and plasma exchange for hypertriglyceridemic pancreatitis.
   - Category IV — Disorders for which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances. Examples: Plasma exchange for active rheumatoid arthritis and pemphigus vulgaris.

2. In a report called plasma exchange in the hyperviscosity syndrome due to immunoglobulins the following is summarized: Patients presenting with severe neurologic impairment, such as stupor or coma, should be treated with plasma exchange (plasmapheresis) on an emergency basis. A reasonable initial prescription would be a one plasma volume exchange, replaced with albumin, repeated daily until symptoms subside or until serum viscosity is normal. [17]

3. In a report called treatment and prognosis of Guillain-Barré syndrome in adults the following is summarized: Large, randomized multicenter trials have established the effectiveness of plasma exchange in patients with severe GBS. Plasma exchange was most effective when started within seven days of symptom onset. Four exchanges were superior to two in patients with moderately severe GBS. However, in subjects with severe disease requiring mechanical ventilation, six exchanges were not superior compared with four. [18]

4. In a report called treatment of anti-GBM antibody (Goodpasture's) disease initial plasmapheresis therapy is recommended for two to three weeks, with serial assessment of anti-GBM titers and clinical status. If the patient still has hemoptysis or positive anti-GBM titers at the end of the two- to three-week regimen, continuation of plasmapheresis is suggested until hemoptysis resolves and anti-GBM titers are markedly suppressed or negative. [19]

5. In a report called treatment of myasthenia gravis plasmapheresis is noted to be an established treatment for seriously ill patients in the midst of myasthenic crisis however it is not a useful long-term treatment because of the need for repeated exchanges often leads to problems with venous access. [20]

6. In a report called treatment of kidney disease in multiple myeloma plasmapheresis is a reasonable therapy for individuals with AKI suspected to be due to cast nephropathy in the following settings: Patients with cast nephropathy on kidney biopsy and in cases with highly suggestive clinical presentations, plasmapheresis may be initiated on the basis of high levels of free monoclonal light chains in the serum or urine, even in the absence of a renal biopsy. This includes patients with myeloma presenting with acute kidney injury and a serum free light chain level of 200 mg/dL or more. [21]

7. In a report called treatment of acute exacerbations of multiple sclerosis in adult's plasma exchange for patients with acute, severe neurologic deficits caused by multiple sclerosis who have a poor response to treatment with high-dose glucocorticoids is recommended. [22]

8. In a report called treatment of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome in adults the superior efficacy of plasma exchange in the treatment of TTP-HUS in adults was outlined in two trials that included 210 patients. Plasma exchange with fresh frozen plasma was more effective than plasma infusion alone. At six months, the remission and survival rates with these two procedures were 78 versus 31 percent (remission) and 78 versus 50 percent (survival). [23]

Professional Organizations

American Society for Apheresis (ASA) [4]: In 2010, the ASA published the fifth special edition of evidence-based guidelines for the practice of apheresis medicine. They classified the indications for apheresis into four categories (I-IV) based on the quality of the evidence and the strength of recommendations derived from the evidence. These categories rate the indications for PP by condition and include the following:

- Category 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. [Example: plasma exchange in Guillain-Barre´ syndrome as first-line standalone therapy; plasma exchange in myasthenia gravis as first-line in conjunction with immunosuppression and cholinesterase inhibition]".
- Category II – "Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment. [Example: plasma exchange as standalone secondary treatment for acute disseminated encephalomyelitis after high-dose IV corticosteroid failure; extracorporeal photopheresis added to corticosteroids for unresponsive chronic graft-versus-host disease]".
- Category III – "Optimum role of apheresis therapy is not established. Decision making should be individualized. [Example: extracorporeal photopheresis for nephrogenic systemic fibrosis; plasma exchange in patients with sepsis and multiorgan failure]".

- Category IV – "Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances. [Example: plasma exchange for active rheumatoid arthritis]".

American Academy of Neurology [8] (2011) published guidelines for plasmapheresis. The guidelines recommend the following:

- Plasmapheresis should be offered in the treatment of AIDP/GBS severe enough to impair independent walking or to require mechanical ventilation.
- Plasmapheresis should be offered as a short-term treatment for patients with CIDP
- Plasmapheresis is probably effective in IgA- and IgG- monoclonal gammopathy of undetermined significance (MGUS)-associated polyneuropathy, based on one Class I study.
- Because of the lack of randomized controlled studies with masked outcomes, there is insufficient evidence to support or refute the efficacy of plasmapheresis in the treatment of myasthenic crisis.
- Plasmapheresis should be considered for the adjunctive treatment of exacerbations in relapsing forms of MS
- Plasmapheresis should be considered in polyneuropathy associated with IgA and IgG MGUS
- Plasmapheresis should not be considered in the treatment of polyneuropathy associated with IgM MGUS
- Based on a single Class II study, plasmapheresis is possibly effective for acute fulminant CNS demyelinating diseases (including MS, acute disseminated encephalomyelitis [ADEM], neuromyelitis optica [NMO], and transverse myelitis [TM]) that fail to respond to high-dose corticosteroid treatment. Because the study included subgroups of patients with demyelinating diseases, it is not possible to determine if plasmapheresis is more or less effective in patients with different demyelinating diseases.
- There is insufficient evidence to support or refute the use of plasmapheresis in the treatment of acute OCD and tic symptoms in the setting of PANDAS.
- There is insufficient evidence to support or refute the use of plasmapheresis in the treatment of Sydenham chorea.

The European Federation of Neurological Societies (EFNS) [6 7] recommended plasmapheresis as a short-term treatment for myasthenia gravis, especially in severe cases to induce remission and in preparation for surgery. EFNS indicated that IVIG and plasmapheresis are equally effective for treatment exacerbations. EFNS recommended plasmapheresis for CIDP when IVIG and corticostereoids are ineffective. Plasmapheresis is also recommended as a consideration for the treatment of IgM paraproteinemic demyelinating neuropathies especially in patients with rapid worsening or clinically similar to typical CIDP, although any benefit may be only short term and repeated treatments may be required.

CODING INFORMATION

CPT	Description
36514	Therapeutic apheresis; for plasmapheresis

HCPCS	Description
S2120	Low density lipoprotein (LDL) apheresis using heparin-induced extracorporeal LDL precipitation

ICD-9	Description
203.00	Multiple myeloma, without mention of having achieved remission
203.02	Multiple myeloma, in relapse
283.0	Autoimmune hemolytic anemias
283.11	Hemolytic-uremic syndrome
284.81	Red cell aplasia (acquired) (adult) (with thymoma)
284.89	Other specified aplastic anemias
287.41	Posttransfusion purpura
289.81	Primary hypercoagulable state
323.61	Infectious acute disseminated encephalomyelitis (ADEM)
323.81	Other causes of encephalitis and encephalomyelitis
340	Multiple sclerosis
341.0	Neuromyelitis optica
341.9	Demyelinating disease of central nervous system, unspecified
356.3	Refsum's disease
357.89	Other inflammatory and toxic neuropathy
358.30-358.39	Lambert-Eaton syndrome
446.4	Wegener's granulomatosis
580.4	Acute glomerulonephritis with lesion of rapidly progressive glomerulonephritis
582.4	Chronic glomerulonephritis with lesion of rapidly progressive glomerulonephritis
583.4	Nephritis and nephropathy, not specified as acute or chronic, with lesion of rapidly progressive glomerulonephritis
584.5	Acute kidney failure with lesion of tubular necrosis
656.10	Rhesus isoimmunization, unspecified as to episode of care or not applicable
656.11	Rhesus isoimmunization, delivered, with or without mention of antepartum condition
656.13	Rhesus isoimmunization, antepartum condition or complication
710.0	Systemic lupus erythematosus
996.81	Complications of transplanted kidney
988.1	Toxic effect of noxious substances eaten as food, mushrooms
V42.0	Organ or tissue replaced by transplant, kidney
V42.1	Organ or tissue replaced by transplant, heart

V42.82	Peripheral stem cells replaced by organ or tissue replaced by transplant, other specified organ or tissue, peripheral stem cells

ICD-10	Description
C90.00	Multiple myeloma not having achieved remission
C90.02	Multiple myeloma in relapse
D59.3	Hemolytic-uremic syndrome
D60.0	Chronic acquired pure red cell aplasia
D60.1	Transient acquired pure red cell aplasia
D60.8	Other acquired pure red cell aplasias
D60.9	Acquired pure red cell aplasia, unspecified
D61.1	Drug-induced aplastic anemia
D61.2	Aplastic anemia due to other external agents
D61.89	Other specified aplastic anemias and other bone marrow failure syndromes
D68.51	Activated protein C resistance
D68.52	Prothrombin gene mutation
D68.59	Other primary thrombophilia
D68.61	Antiphospholipid syndrome
D68.62	Lupus anticoagulant syndrome
D69.51	Posttransfusion purpura
G04.00	Acute disseminated encephalitis and encephalomyelitis, unspecified
G04.01	Postinfectious acute disseminated encephalitis and encephalomyelitis (postinfectious ADEM)
G04.39	Other acute necrotizing hemorrhagic encephalopathy
G04.81	Other encephalitis and encephalomyelitis
G35	Multiple sclerosis
G36.0	Neuromyelitis optica [Devic]
G37.9	Demyelinating disease of central nervous system, unspecified
G60.1	Refsum's disease
G61.89	Other inflammatory polyneuropathies
G70.80	Lambert-Eaton syndrome, unspecified
M31.30	Wegener's granulomatosis without renal involvement
M32.10	Systemic lupus erythematosus, organ or system involvement unspecified
N01.3	Rapidly progressive nephritic syndrome with diffuse mesangial proliferative glomerulonephritis
N03.8	Chronic nephritic syndrome with other morphologic changes
N05.9	Unspecified nephritic syndrome with unspecified morphologic changes
N17.0	Acute kidney failure with tubular necrosis
O36.0110	Maternal care for anti-D [Rh] antibodies, first trimester, not applicable or unspecified
O36.0120	Maternal care for anti-D [Rh] antibodies, second trimester, not applicable or unspecified
O36.0130	Maternal care for anti-D [Rh] antibodies, third trimester, not applicable or unspecified
O36.0910	Maternal care for other rhesus isoimmunization, first trimester, not applicable or unspecified

O36.0920	Maternal care for other rhesus isoimmunization, second trimester, not applicable or unspecified
O36.0930	Maternal care for other rhesus isoimmunization, third trimester, not applicable or unspecified
T62.0X1A	Toxic effect of ingested mushrooms, accidental (unintentional), initial encounter
T62.0X2A	Toxic effect of ingested mushrooms, intentional self-harm, initial encounter
T62.0X3A	Toxic effect of ingested mushrooms, assault, initial encounter
T62.0X4A	Toxic effect of ingested mushrooms, undetermined, initial encounter
T86.10	Unspecified complication of kidney transplant
T86.11	Kidney transplant rejection
T86.12	Kidney transplant failure
Z94.0	Kidney transplant status
Z94.1	Heart transplant status
Z94.84	Stem cells transplant status

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