Kansas City

An Independent Licensee of the Blue Cross and Blue Shield Association

Plasma Exchange

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Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for plasma exchange when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered

Plasma exchange is considered **medically necessary** for the conditions listed below:

Autoimmune

- Severe multiple manifestations of mixed cryoglobulinemia (MC) such as cryoglobulinemic nephropathy, skin ulcers, sensory motor neuropathy, and widespread vasculitis in combination with immunosuppressive treatment;
- catastrophic antiphospholipid syndrome (CAPS).

Hematologic

- ABO incompatible hematopoietic progenitor cell transplantation;
- hyperviscosity syndromes associated with multiple myeloma or Waldenstrom's macroglobulinemia;
- idiopathic thrombocytopenic purpura in emergency situations;
- thrombotic thrombocytopenic purpura (TTP);
- atypical hemolytic-uremic syndrome;
- post-transfusion purpura;
- HELLP syndrome of pregnancy (a severe form of preeclampsia, characterized by hemolysis [H], elevated liver enzymes [EL], and low platelet [LP] counts);
- myeloma with acute renal failure.

Neurological

- acute inflammatory demyelinating polyneuropathy (Guillain-Barre syndrome; severity grade 1-2 within two weeks of onset; severity grade 3-5 within four weeks of onset; and children less than 10 years old with severe GBS
- chronic inflammatory demyelinating polyradiculoneuropathy (CIDP);
- multiple sclerosis (MS), with acute fulminant central nervous system (CNS) demyelination
- myasthenia gravis in crisis or as part of preoperative preparation;
- paraproteinemia polyneuropathy; IgA, IgG;

Renal

- Anti-glomerular basement membrane disease (Goodpasture's syndrome);
- ANCA [antineutrophil cytoplasmic antibody]-associated vasculitis [e.g., Wegener's granulomatosis [also known as granulomatosis with polyangitis (GPA)] with associated renal failure;
- dense deposit disease with factor H deficiency and/or elevated C3 Nephritic factor.

Transplantation

- ABO incompatible solid organ transplantation;
    - Kidney;
    - Heart (infants); and

- renal transplantation: antibody mediated rejection; HLA desensitization;
- focal segmental glomerulosclerosis after renal transplant.

When Policy Topic is not covered

Plasma exchange is considered **investigational** in all other conditions, including, but not limited, to the following:

- ABO incompatible solid organ transplant; liver;
- acute disseminated encephalomyelitis;
- acute inflammatory demyelinating polyneuropathy (Guillain-Barre syndrome) in children less than 10 years old with mild or moderate forms
- acute liver failure;
- amyotropic lateral sclerosis;
- ANCA-associated rapidly progressive glomerulonephritis (Wegener's granulomatosis);
- aplastic anemia;
- asthma;
- autoimmune hemolytic anemia; warm autoimmune hemolytic anemia; cold agglutinin disease;
- chronic fatigue syndrome;
- coagulation factor inhibitors;
- cryoglobulinemia; except for severe mixed cryoglobulinemia as noted above
- dermatomyositis and polymyositis;
- focal segmental glomerulosclerosis (other than after renal transplant);
- heart transplant rejection treatment;
- hemolytic uremic syndrome (HUS); typical (diarrheal-related);
- hyperviscoscity syndromes with renal failure (other than associated with multiple myeloma or Waldenstrom's macroglobulinermia);
- idiopathic thrombocytopenic purpura; refractory or non-refractory;
- inclusion body myositis;
- Lambert-Eaton myasthenic syndrome;
- multiple sclerosis; chronic progressive or relapsing remitting;
- mushroom poisoning;
- myasthenia gravis with anti-MuSK antibodies;
- overdose and poisoning (other than mushroom poisoning);
- paraneoplastic syndromes;
- paraproteinemia polyneuropathy; IgM
- pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)
- pemphigus vulgaris;
- phytanic acid storage disease (Refsum's disease);
- POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes);
- psoriasis;
- red cell alloimmunization in pregnancy;
- rheumatoid arthritis;
- sepsis;
- scleroderma (systemic sclerosis);
- stiff person syndrome;
- Sydenham's chorea (SC);
- systemic lupus erythematosus; manifestations other than nephritis; nephritis; and
- thyrotoxicosis.

Considerations

Patients receiving plasma exchange (PE) as a treatment of CIDP should meet the diagnostic criteria for CIDP, which are included in an Appendix to this policy.

The use of PE in patients with acute, life-threatening complications of chronic autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus (SLE), may need to be considered on

an individual basis. An example of such a situation would be the development of a severe vasculitis, in which it is hoped that the use of PE can acutely lower the level of serum autoantibodies until an alternate long-term treatment strategy can be implemented. However, in these situations, the treatment goals and duration of treatment with PE need to be clearly established prior to its initiation; without such treatment goals, the use of an acute short-term course of PE may insidiously evolve to a chronic use of PE with uncertain benefit.

Description of Procedure or Service

Plasma exchange (PE) is a procedure in which the plasma is isolated, then discarded and replaced with a substitution fluid such as albumin. PE is a nonspecific therapy, because the entire plasma is discarded. PE has been used in a wide variety of acute and chronic conditions, as well as in the setting of solid organ transplantation.

Background/Overview
The terms therapeutic apheresis, plasmapheresis, and plasma exchange are often used interchangeably but when properly used denote different procedures. The American Society for Apheresis (ASFA) definitions for these procedures are as follows:

Apheresis: A procedure in which blood of the patient or donor is passed through a medical device which separates out one or more components of blood and returns remainder with or without extracorporeal treatment or replacement of the separated component.

Plasmapheresis: A procedure in which blood of a patient or the donor is passed through a medical device which separates out plasma from the other components of blood and the plasma is removed (i.e., less than 15% of total plasma volume) without the use of replacement solution.

Plasma exchange: A therapeutic procedure in which blood of the patient is passed through a medical device which separates out plasma from other components of blood, the plasma is removed and replaced with a replacement solution such as colloid solution (e.g., albumin and/ or plasma) or combination of crystalloid/colloid solution.

This policy addresses only plasma exchange as a therapeutic apheresis procedure.

The rationale for PE is based on the fact that circulating substances, such as toxins or autoantibodies, can accumulate in the plasma. Also, it is hypothesized that removal of these factors can be therapeutic in certain situations. Plasma exchange is essentially a symptomatic therapy, since it does not remove the source of the pathogenic factors. Therefore the success of PE will depend on whether the pathogenic substances are accessible through the circulation, and whether their rate of production and transfer to the plasma component can be adequately addressed by PE. For example, PE can rapidly reduce levels of serum autoantibodies; however, through a feedback mechanism, this rapid reduction may lead to a rebound overproduction of the same antibodies. This rebound production of antibodies is thought to render the replicating pathogenic clone of lymphocytes more vulnerable to cytotoxic drugs; therefore, PE is sometimes used in conjunction with cyclophosphamide.

Applications of PE can be broadly subdivided into 2 general categories: 1) acute self-limited diseases, in which PE is used to acutely lower the circulating pathogenic substance; and 2) chronic diseases, in which there is ongoing production of pathogenic autoantibodies. Because PE does not address underlying pathology, and, due to the phenomenon of rebound antibody production, its use in chronic diseases has been more controversial than in acute self-limited diseases.

In addition, plasmapheresis has been used in the setting of solid organ transplantation. It has been used as a technique to desensitize high-risk patients prior to transplant and also as a treatment of antibody-mediated rejection reaction (AMR) occurring after transplant. Prior to transplant, plasmapheresis has been most commonly used to desensitize patients receiving an ABO mismatched

kidney, often in combination with a splenectomy. As a treatment of AMR, plasmapheresis is often used in combination with intravenous immunoglobulin (IVIg) or anti-CD-20 therapy (i.e., Rituxan).

Rationale

This policy was originally created in 1995 and was updated regularly with searches of the MEDLINE database. The most recent literature review was performed through April 3, 2014. Following is a summary of the key literature to date:

Autoimmune Diseases

One potential type of evidence in support of the clinical effectiveness of plasma exchange (PE) in treating autoimmune diseases is the identification of a pathogenic component of plasma that is reliably eliminated by plasmapheresis.(1) Although many laboratory abnormalities are associated with autoimmune connective tissue diseases, it is unclear which, if any, cause the clinical manifestations of the disease. Furthermore, it is not known to what extent plasma levels parallel clinical disease. For example, in many of the controlled trials discussed as follows, PE reliably reduced circulating autoantibodies and immune complexes, but without demonstrable clinical benefit. It may be that the patient had already suffered irreversible damage or that the pathogenesis of the disease was a local process unrelated to circulating factors. Over the past 10 years, randomized trials of PE have been conducted and, in general, have shown a lack of effectiveness as treatment of chronic autoimmune diseases. Clinical results of randomized trials of plasmapheresis for specific chronic autoimmune diseases are discussed here.

Systemic Lupus Erythematosus

Reporting on the results of a randomized controlled trial (RCT), Lewis et al concluded that PE had no benefit in patients with systemic lupus and glomerulonephritis compared with a standard therapy regimen of prednisone and cyclophosphamide.(2) Plasmapheresis has also been investigated as a technique to improve the effectiveness of cyclophosphamide therapy. For example, it is thought that the acute lowering of pathogenic autoantibodies with plasmapheresis may result in their rebound production. It is hoped that the pathogenic lymphocytes would be more sensitive to cyclophosphamide at this point. Danieli et al reported on a prospective nonrandomized trial of 28 patients with proliferative lupus nephritis; 12 underwent synchronized plasmapheresis and pulse cyclophosphamide therapy, while the remaining 16 underwent cyclophosphamide alone.(3) While plasmapheresis was associated with a decreased time to remission of renal disease, at the end of the 4-year follow-up, there was no difference in outcome.

Multiple Sclerosis

There have been several RCTs of PE in patients with multiple sclerosis (MS) that have reported inconclusive results. Khatri et al studied 54 patients with chronic progressive MS randomized to receive sham or true PE.(4) The degree of improvement in the PE group was greater than that in the control group. Weiner et al reported on a study that randomized patients with acute attacks of MS to receive either PE or sham treatments; there was no statistical difference in improvement between groups, although patients receiving PE did have a faster recovery rate from acute attacks.(5) A Canadian trial randomized 168 patients with progressive MS to receive either PE or immunosuppressive therapy.(6) There were no significant differences in the rates of treatment failures between groups.

Lambert-Eaton Myasthenic Syndrome and Other Paraneoplastic Syndromes

Paraneoplastic neuromuscular syndromes are characterized by the production of tumor antibodies that cross-react with the patient's nervous system tissues. Lambert-Eaton myasthenic syndrome (LEMS), characterized by proximal muscle weakness of the lower extremities and associated most frequently with small cell lung cancer, is the most common paraneoplastic syndrome. The presumed autoimmune nature of LEMS and other paraneoplastic syndromes led to the use of a variety of immunomodulatory

therapies, including PE. However, there are minimal data in the published literature and no controlled trials. The largest case series focusing on LEMS was reported by Tim et al and included 73 patients with LEMS, 31 of whom were found to have lung cancer.(7) Although detailed treatment strategies are not provided, 19 underwent plasmapheresis, with 27% reporting a moderate to marked response. However, the improvement after plasmapheresis, even when marked was only transient. Patients also received other therapies, for example, various chemotherapy regimens for the underlying lung cancer. In addition, 53 of the 73 patients received 3,4 diaminopyridine, with 79% reporting marked or moderate responses. A small RCT of 3,4 diaminopyridine has also reported positive results, confirming other anecdotal reports.(8) Anderson et al reported on a case series of 12 patients with paraneoplastic cerebellar degeneration. Although plasmapheresis was associated with an acute drop in the autoantibody titer, only 2 patients showed a minor improvement in neurologic symptoms.(9)

Rheumatoid Arthritis

In 1983, Dwosh et al reported on 26 patients with chronic rheumatoid arthritis randomized in a crossover design to either true or sham PE. The authors concluded that PE did not have any clinical benefit, despite impressive laboratory changes.(10)

Polymyositis/Dermatomyositis

Miller and colleagues conducted a randomized trial of PE in the treatment of 39 patients with polymyositis and dermatomyositis and found that it was no more effective than sham pheresis.(11)

Pemphigus

Pemphigus is an autoimmune blistering skin disease that is characterized by serum antibodies that bind to squamous epithelia. Steroids or other immunosuppressants are the most common forms of treatment, but the high doses of steroids can produce significant adverse effects. Guillaume et al reported on a study of 40 patients with pemphigus randomized to receive either prednisone alone or prednisone plus plasmapheresis.(12) The goal of the study was to determine whether plasmapheresis could reduce the required dose of steroids, thus limiting its toxicity. Unfortunately, disease control in the 2 groups was the same, and the authors concluded that plasmapheresis in conjunction with low-dose steroids is not effective in treating pemphigus.

Stiff Man (or Stiff Person) Syndrome

Stiff man syndrome is an autoimmune disorder characterized by involuntary stiffness of axial muscles and intermittent painful muscle spasm. Stiff man syndrome may be idiopathic in nature or seen in association with thymoma, Hodgkin disease, and small cell lung; colon; or breast cancer. The mainstay of treatment of stiff man syndrome is diazepam. The published literature regarding plasmapheresis consists of small case series and anecdotal reports.(13-16) Most of these studies were published in the late 1980s or early 1990s; 1 case series with 9 patients was published in 2014.(16)

Cryoglobulinemia

There are several types of cryoglobulinemia. Type I is associated with hematologic disorders. Types II and III are considered mixed cryoglobulins. Mixed cryoglobulin syndrome is a consequence of immune-complex mediated vasculitis and may be associated with infectious and systemic disorders (eg, hepatitis C virus). In 2010, Rockx and Clark published a review of studies evaluating PE for treating cryoglobulinemia that included at least 5 patients.(17) They identified 11 studies with a total of 156 patients. The authors concluded, “The quality and variability of the evidence precludes a meta-analysis or even a systematic analysis. However, these studies weakly support the use of plasma exchange largely on a mechanistic basis.”

Hematologic

Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome

Once considered distinct syndromes, thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are now considered different manifestations of the same disease process, ie, thrombotic microangiopathy. In 2009, a systematic review evaluated the benefits and harms of different interventions for HUS and TTP (separately).(18) Interventions were compared with placebo or supportive therapy or a comparison of 2 or more interventions. Interventions examined included heparin, aspirin/dipyridamole, prostanoids, ticlopidine, vincristine, fresh frozen plasma (FFP) infusion, plasmapheresis with FFP, systemic corticosteroids, Shiga toxin-binding agents, or immunosuppressive agents. For TTP, 6 RCTs (n=331) were identified evaluating PE with FFP as the control. Interventions tested included antiplatelet therapy plus PE with FFP, FFP transfusion, and PE with cryosupernatant plasma. Two studies compared plasma infusion (PI) to PE with FFP and showed a significant increase in failure of remission at 2 weeks (risk ratio [RR], 1.48) and all-cause mortality (RR=1.91) in the PI group. The authors concluded that PE with FFP is the most effective treatment available for TTP. Seven RCTs included children with HUS. None of the assessed interventions was superior to supportive therapy alone for all-cause mortality, neurologic/extrarenal events, renal biopsy changes, proteinuria, or hypertension at the last follow-up visit. Bleeding was significantly higher in those receiving anticoagulation therapy compared with supportive therapy alone (RR=25.89). For patients with HUS, supportive therapy including dialysis was the most effective treatment. All studies in HUS have been conducted in the diarrheal 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. A recent review article by Noris and Remuzzi describes the data supporting use of PE in the atypical form of this disease, with results showing remission in up to 60% of patients.(19)

Because the available evidence for patients with typical HUS shows supportive therapy, including dialysis, to be the most effective treatment, all studies in HUS have been conducted with patients with the diarrheal (typical) form of the disease; the use of PE for the treatment of typical HUS is inadequate to draw clinical conclusions. PE for HUS was considered medically necessary in previous updates. PE remains medically necessary for atypical HUS.

Idiopathic Thrombocytopenic Purpura

Idiopathic thrombocytopenic purpura is an acquired disease of either adults or children characterized by the development of autoantibodies to platelets. Management of acute bleeding due to thrombocytopenia typically involves immediate platelet transfusion, occasionally in conjunction with a single infusion of intravenous immunoglobulin (IVIg). PE has been occasionally used in emergency situations.

Posttransfusion Purpura

Posttransfusion purpura is a rare disorder characterized by an acute severe thrombocytopenia occurring about 1 week after a blood transfusion in association with a high titer of antiplatelet alloantibodies. Because of its rapid effect, PE is considered the initial treatment of choice.

HELLP Syndrome of Pregnancy

The HELLP syndrome of pregnancy (characterized by hemolysis [H], elevated liver enzymes [EL], and low platelet [LP] counts) is a severe form of preeclampsia, characterized by hemolysis, elevated liver enzymes, and low platelet counts. The principal form of treatment is delivery of the fetus. However, for patients with severe thrombocytopenia, PE may be indicated if the fetus cannot safely be delivered, or if the maternal thrombocytopenia persists into the postnatal period.

Neurologic

Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) is an acute demyelinating neuropathy whose severity is graded on a scale of 1 to 5 (the disability scale is summarized in the Appendix to this policy). In 2012, The Cochrane Collaboration published an updated systematic review of the evidence concerning the efficacy of PE for treating GBS.(20) Six eligible trials (n=649) were identified comparing PE versus supportive treatment alone. No additional trials were published since the 2002 review. The primary outcome measures of the review included time to recover walking with aid and time to onset of motor recovery in mildly affected patients. A pooled analysis of data from 3 trials found that PE significantly increased the proportion of patients who recovered the ability to walk with assistance after 4 weeks (RR=1.60; 95% confidence interval [CI], 1.19 to 2.15). Data on time to onset of motor recovery were not pooled. Pooled analyses found that PE led to significant improvement in secondary outcomes including reduced time to recover walking without aid, increased likelihood of full muscle strength recovery and reduced likelihood of severe motor sequelae. However, there was a significantly higher risk of relapse in the group that received PE compared with supportive treatment alone (RR=2.89; 95% CI, 1.05 to 7.93; 6 trials).

A 2007 systematic review evaluated the available randomized trials of immunotherapy to treat GBS.(21) In 4 trials with severely affected adult participants (n=585), those treated with PE improved significantly more on the disability scale 4 weeks after randomization than those who were not (weighted mean difference [WMD], -0.89; range, -1.14 to -0.63). In 5 trials (n=582), the improvement on the disability grade scale with IVIg was very similar to that with PE (WMD= -0.02; range, -0.25-0.20). There was also no significant difference between IVIg and PE for any of the other outcome measures. There was 1 trial that included patients (n=91) with the mild form of GBS who were able to walk unaided at enrollment. Patients were randomized to receive either 2 sessions of PE in 3 days or supportive care. The number of patients with 1 or more grades of improvement at 1 month was significantly greater, 26 of 45 in the treated compared with the control group, 13/45. Fewer patients in the PE-treated group had clinical deterioration (4%) compared with the control group (39%) or required ventilation; PE group (2%) versus the control group (13%). In 1 trial (n=148), following PE with IVIg, did not produce significant extra benefit. Limited evidence from 3 open trials in children suggested that IVIg hastens recovery compared with supportive care alone. None of the treatments significantly reduced mortality. The authors concluded that “since approximately 20% of patients die or have persistent disability despite immunotherapy, more research is needed to identify better treatment regimens and new therapeutic strategies.”

In 2003, a report of the Quality Standards Subcommittee of the American Academy of Neurology (AAN), *Practice parameter: immunotherapy for Guillain-Barré syndrome,* was published.(22) The following are the key findings: (1) treatment with PE or IVIg hastens recovery from GBS; (2) combining the 2 treatments is not beneficial; and (3) steroid treatment given alone is not beneficial. The AAN’s recommendations are: (1) PE is recommended for nonambulant adult patients with GBS who seek treatment within 4 weeks of the onset of neuropathic symptoms (PE should also be considered for ambulant patients examined within 2 weeks of the onset of neuropathic symptoms); (2) IVIg is recommended for nonambulant adult patients with GBS within 2 or possibly 4 weeks of the onset of neuropathic symptoms (the effects of PE and IVIg are equivalent); (3) corticosteroids are not recommended for the management of GBS; (4) sequential treatment with PE followed by IVIg, or immunoabsorption followed by IVIg is not recommended for patients with GBS; and (5) PE and IVIg are treatment options for children with severe GBS.

A 2011 RCT from Iran addresses PE for treating young children with severe GBS.(23) The study included 41 children with GBS who required mechanical ventilation and had muscle weakness for no more than 14 days. Patients were randomized to receive PE (n=21) or IVIg (n=20). Mean age of the patients was 96 months in the PE group and 106 months in the IVIg group. Duration of ventilation, the primary outcome, was a mean (SD) of 11 (1.5) days in the PE group and 13 (2.1) days in the IVIg group (p=0.037). Duration of stay in the intensive care unit, a secondary outcome, was 15.0 (2.6) days in the PE group and 16.5 (2.1) days in the IVIg group (p=0.94).

In conclusion, the available evidence is sufficient regarding PE for the treatment of patients with all severity grades of GBS. This therapy has a beneficial impact on net health outcome for all severity

grades. The published studies are insufficient regarding PE for treatment of GBS in the pediatric population. However, based on limited published data, as well as extrapolated data from studies in adults and clinical input, PE may be considered as a treatment option for children younger than 10 years old with severe GBS.

Chronic Inflammatory Demyelinating Polyradiculoneuropathy

A 2012 Cochrane review by Mehnidiratta and Hughes identified 2 randomized trials on PE for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).(24) Both trials were considered to be of high quality, but both had small sample sizes. One trial with 29 patients used a parallel design and compared PE with sham treatment. The other study included 15 patients and used a crossover design to compare PE and sham treatment. A pooled analysis of data from the 2 trials found a statistically significantly greater improvement in impairment after 4 weeks with PE versus sham (mean difference, 31 points on the Neuropathy Impairment Score; 95% CI, 16 to 45 points). The scale ranges from 0 (normative) to 280 (maximally affected). Data on other outcomes were not suitable for pooled analysis.

Acute Fulminant Central Nervous System Demyelination

The policy statement, which suggests that plasmapheresis may be considered medically necessary in patients with acute fulminant CNS demyelination, is based on the results of a randomized, double-blinded trial, in which 22 patients with MS or other acute idiopathic inflammatory demyelinating diseases of the CNS were enrolled a minimum of 14 days after having failed to respond to at least 5 days of high-dose corticosteroids.(25) Patients were randomized to receive either 7 real or sham PE procedures over a 14-day period. The primary outcome was a targeted neurologic deficit (ie, aphasia, cognitive dysfunction). Overall, moderate to marked improvement of the targeted outcome was obtained in 42% of the treatment group, compared with only 6% in the placebo group.

Paraproteinemic Polyneuropathies

A randomized, double-blinded trial compared PE with sham treatment in 39 patients with monoclonal gammopathy of undetermined significance (MGUS)–associated polyneuropathy.(26) After twice weekly PE for 3 weeks, the treatment group reported improvements in neurologic function in the IgG and IgA groups but not the IgM MGUS groups. In addition, those from the sham group who were later crossed over to the PE group also reported improvement.

Myasthenia Gravis

Several RCTs have been published. One of these, a 2011 trial from Germany, included patients with myasthenic crisis.(27) Patients were randomized to treatment with PE (n=10) or immunoadsorption (IA) (n=9). In both groups, 3 apheresis treatments were performed within 7 days; patients could have additional treatments if needed. A total of 16 of 19 (84%) of patients, 8 in each group, completed the study and were included in the efficacy analysis. The mean number of treatments was 3.5 in the PE group and 3.4 in the IA group ($p>0.05$). The primary outcome was change in the modified clinical score (maximum of 3 points) on day 14 after the last treatment. The baseline modified clinical score was 2.6 in the PE group and 2.5 in the IA group. At day 14, score improvement was 1.6 points in the PE group and 1.4 points in the IA group ($p>0.05$). Within the 180 days after treatment, 1 patient in the PE group and 3 patients in the IA group experienced another myasthenic crisis; the number of events was too small for meaningful statistical analysis for this outcome. There were no statistically significant differences in outcomes in this study, but the sample was very small and the study was probably underpowered.

Two trials included patients with myasthenia gravis in the absence of myasthenic crisis. A randomized trial from China was published in 2009.(28) Liu et al assigned 40 patients with late-onset myasthenia gravis to treatment with double-filtration plasmapheresis (n=15), IA (n=10), or intravenous immune globulin (n=15). Treatment was clinically effective, defined as at least a 50% improvement in the

relative symptom score, in 12 of 15 (80%) of the plasmapheresis group, 7 of 10 (70%) in the IA group, and 6 of 15 (40%) of the immune globulin group. The clinical efficacy rate was significantly higher in both the plasmapheresis and immunoadsorption groups compared with the immune globulin group ($p<0.05$). Findings were similar for other outcomes; the study was limited by the small sample size. A 2011 trial by Barth et al in Canada randomized patients with myasthenia gravis to treatment with PE (n=43) or IVIg (n=41).(29) Patients had moderate to severe myasthenia gravis, as defined by a score of at least 10.5 on the Quantitative Myasthenia Gravis Score (QMGS) for disease severity, and worsening weakness requiring a change in treatment. Patients were not experiencing myasthenic crisis. At day 14, there was not a statistically significant difference between groups in the change on the QMGS, the primary efficacy outcome. Mean QMGSs at day 14 were 4.7 in the PE group and 3.2 in the IVIg group ($p=0.13$). Moreover, at day 14, 69% were considered improved on PE versus 65% in IVIg; the difference between groups was not statistically significant ($p=0.74$). Safety outcomes were published in 2013.(30) Forty-two patients received a total of 203 PE procedures; 40 completed the full course of 5 procedures. Complications occurred in 19 of 42 patients (45%). Two of the complications were serious. One patient had hypertension, heart failure, and pneumonia; all of these were unrelated to the procedures. The other patient had a myocardial infarction, which could have been exacerbated by PE.

The results from the few trials evaluating treatment of myasthenia gravis suggest that PE is reasonably safe in patients with moderate to severe myasthenia crisis. There is some evidence on the comparative efficacy of PE versus IVIg, but the trials are small and report mixed results, and therefore definitive conclusions cannot be made.

Renal

Rapidly Progressive Glomerulonephritis

Rapidly progressive glomerulonephritis (RPGN) is a general term describing the rapid loss of renal function in conjunction with the finding of glomerular crescents on renal biopsy specimens. There are multiple etiologies of RPGN including vasculitis, the deposition of antiglomerular basement membrane antibodies, as seen in Goodpasture syndrome, or the deposition of immune complexes, as seen in various infectious diseases or connective tissue diseases. PE has long been considered a treatment alternative in immune-mediated RPGN. However, there have been few controlled clinical trials published, and their interpretation is difficult due to the small number of patients, choice of intermediate outcomes (ie, the reduction in antibody levels as opposed to more direct patient outcomes), and heterogeneity in patient groups.(31) Aside from cases of Goodpasture disease, the rationale for PE in idiopathic RPGN is not as strong, because of the lack of an identifiable immune component. Studies of PE in this population have not demonstrated a significant improvement in outcome compared with the use of pulse steroid therapy.(32)

Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

In 2011, Walsh et al published a meta-analysis of studies on PE in adults with the diagnosis of either idiopathic renal vasculitis or rapidly progressive glomerulonephritis.(33) A total of 9 trials including 387 patients were identified. The clinical populations in the studies were somewhat ill-defined, but most patients appeared to have antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis. In a pooled analysis of study findings, there was a significantly lower risk of end-stage renal disease in patients treated with adjunctive PE compared with standard care alone (RR=0.64; 95% CI, 0.47 to 0.88). The risk of death did not differ significantly in the 2 groups (RR=1.01; 95% CI, 0.71 to 1.40).

A relatively large RCT, included in the previously mentioned meta-analysis, was published in 2007 by Jayne et al.(34) This was a multicenter trial conducted on behalf of the European Vasculitis Study Group. The study investigated whether the addition of PE was more effective than intravenous methylprednisolone. Patients (n=137) with a new diagnosis of ANCA-associated systemic vasculitis confirmed by renal biopsy and serum creatinine greater than 500 µmol/L (5.8 mg/dL) were randomly assigned to receive 7 PEs (n=70) or 3000 mg of intravenous methylprednisolone (n=67). Both groups

received oral cyclophosphamide and oral prednisolone. The primary end point was dialysis independence at 3 months. Secondary end points included renal and patient survival at 1 year and severe adverse event rates. At 3 months, 33 (49%) of 67 were alive and independent of dialysis after intravenous methylprednisolone, compared with 48 (69%) of 70 after PE. Compared with intravenous methylprednisolone, PE was associated with a reduction in risk for progression to end-stage renal disease of 24% at 12 months. At 1 year, the patient survival rate was 51 (76%) of 67 in the intravenous methylprednisolone group; 51 (73%) of 70 in the PE group; severe adverse event rates, 32 of 67 (48%) in the intravenous methylprednisolone group; 35 of (50%) 70 in the PE group. PE increased the rate of renal recovery in ANCA-associated systemic vasculitis that presented with renal failure when compared with intravenous methylprednisolone. Patient survival and severe adverse event rates were similar in both groups. Long-term outcomes of patients from the Jayne et al trial were published in 2013.(35) Median follow-up was 3.95 years. A total of 70 of 136 patients had died, 35 (51%) in the PE group and 35 (51%) in the IV methylprednisolone group; the difference between groups was not statistically significant (p=0.75). Similarly, there was not a statistically significant difference between groups in the proportion of patients with end-stage renal disease (33% in the PE group vs 49% in the IV methylprednisolone group, p=0.08). According to findings of this trial, PE appears to have a short-term benefit on preserving renal function in this population, but long-term efficacy remains uncertain.

Transplantation

Solid Organ Transplant

Before 2006, plasmapheresis in the setting of solid organ transplant was not addressed by this policy. However, plasmapheresis has been extensively used in this setting, both as pretransplant prophylaxis (ie, desensitization) for highly sensitized patients at high risk of antibody-mediated rejection (AMR), and as a treatment of AMR after transplant. Desensitization protocols vary among transplant centers; 2 commonly used protocols are referred to as the Cedars-Sinai protocol and the Johns Hopkins protocol. The Cedars-Sinai protocol consists of high-dose IVIg (2 g/kg) and is offered to patients awaiting either a deceased or live donor. The Johns Hopkins protocol consists of low-dose IVIg (100 mg/kg) in combination with plasmapheresis with or without treatment with anti-CD-20 (ie, Rituxan). Plasmapheresis is more commonly used in patients receiving a living kidney transplant from an ABO mismatched donor.(36) A variety of protocols have also been developed for the treatment of AMR, often in combination with other therapies, such as IVIg or anti-CD-20 (eg, (37-40)). Most studies of plasmapheresis in the transplant setting are retrospective case series from single institutions. Therefore, it is not possible to compare immunomodulatory regimens to determine their relative efficacy. Nevertheless, in part based on the large volume of literature published on this subject, it appears that plasmapheresis is a component of the standard of care for the management of AMR.

Other Conditions or Applications

Asthma

There has been some research interest in the use of plasmapheresis in patients with severe, steroid-dependent asthma. However, preliminary results do not suggest treatment effectiveness.(41)

Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections and Sydenham Chorea

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) is defined as rapid, episodic onset of obsessive-compulsive disorder (OCD) and/or tic disorder symptoms after a group A β-hemolytic streptococcal infection (GABHS). Sydenham chorea (SC) is the neurologic manifestation of acute rheumatic fever. The choreatic symptoms of SC are characterized by involuntary rapid and jerky movements that affect the extremities, trunk, and face. SC is generally a self-limited disorder with symptoms resolving in weeks to months. Perlmutter et al conducted an RCT to evaluate the effectiveness of PE and IVIg in reducing the severity of neuropsychiatric symptoms in children

diagnosed in the PANDAS subgroup.(42) Children (n=30) with clear evidence of a strep infection as the trigger of their OCD and tics were randomized to receive PE (n=10; 5-6 procedures over 2 weeks), IVIg (n=9; 2 gm/kg over 2 days,) or placebo (n=10; mimic IVIg). All were severely ill at the time of treatment. At 1 month, both active treatment groups demonstrated symptom improvement, but those in the placebo group were unchanged. The treatment effect was still apparent after 1 year. However, 50% of the children were on the same or higher doses of their baseline medications; thus it is not entirely clear that IVIg or PE had a beneficial effect. This study needs to be replicated with a larger number of patients. The authors noted that children in the placebo group (IVIg control group) subsequently received PE in an open trial and had only minor improvements.

Garvey et al conducted an RCT designed to determine if IVIg or PE would be superior to prednisone in decreasing the severity of chorea.(43) Children with SC (n=18) were randomized to treatment with PE (n= 8; 5-6 procedures over 1-2 weeks), IVIg (n=4; 2 g/kg over 2 days), or prednisone (n=6; 1 mg/kg/d for 10 days followed by taper over next 10 days). The primary outcome was chorea severity at 1 month. The secondary outcome variable was chorea severity at 1 year following treatment. There was no significant difference between the baseline chorea severity scores by the treatment group. Chorea severity was assessed at baseline and at 1, 2, 3, 6, and 12 months following treatment. The chorea rating scale scores range from 0 (no chorea) to 18 (severe or paralytic chorea). A score of 9 or higher was required for study entry. Baseline medications to control choreatic symptoms were discontinued 1 week before baseline assessment and each follow-up evaluation. Mean chorea severity for the entire group was lower at the 1-month follow-up evaluation (overall 48% improvement). The between-group differences were not statistically significant. Larger studies are needed to confirm these clinical observations.

Clinical Input Received Through Physician Specialty Societies and Academic Medical Centers

In response to requests, input was received through 2 physician specialty societies and 3 academic medical centers while this policy was under review in 2012. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. There was consensus or near-consensus that PE for dense deposit disease with Factor H deficiency and/or elevated C3 nephritis factor, catastrophic antiphospholipid syndrome, focal segmental glomerulosclerosis after renal transplant, and myeloma with acute renal failure may be considered medically necessary. Clinical input was mixed on the medical necessity of hyperviscosity syndromes with renal failure (other than associated with multiple myeloma or Waldenström macroglobulinemia). In addition, there was no consensus about an optimal creatinine threshold for instituting PE in patients with renal failure associated with ANCA-associated vasculitis or other diagnoses.

Summary

In conclusion, due to data from published studies and/or clinical support, plasma exchange is considered medically necessary for selected conditions. For conditions in which there is a lack of efficacy data and clinical support, plasma exchange is considered investigational.

Practice Guidelines and Position Statements

The 2014 National Comprehensive Cancer Network guideline on multiple myeloma stated that plasmapheresis is an adjunctive treatment for patients being treated for multiple myeloma who cannot be treated with stem-cell transplant. Primary treatments include chemotherapy, targeted therapy, and steroids given alone or in combination.(44)

In 2011, the American Academy of Neurology (Therapeutics and Technology Assessment Subcommittee) issued an evidence-based guideline on plasmapheresis in the treatment of neurologic disorders.(45) The primary conclusions based on their evidence review are as follows:

- Established effective
  - Acute inflammatory demyelinating polyneuropathy/ Guillain-Barré syndrome
  - Chronic inflammatory demyelinating polyneuropathy, short-term treatment
- Probably effective
  - Relapses in multiple sclerosis
- Possibly effective
  - Fulminant demyelinating CNS disease
- Established ineffective
  - Chronic or secondary progressive multiple sclerosis
- Insufficient evidence
  - Myasthenia gravis
  - Sydenham's chorea
  - Acute obsessive-compulsive disorder and tics in PANDAS

In 2013, the American Society for Apheresis (ASFA) released updated guidelines on the use of therapeutic apheresis.(46) Previously, the guidelines had been updated in 2010 and treatment categories were introduced in a 2007 guideline.(47) The following is a description of the ASFA categories and categories:

Category	Description
I	Category I includes diseases for which TA (therapeutic apheresis) is accepted as first-line treatment, either as a primary standalone treatment or in conjunction with other treatments. Note that this designation need not imply that TA is mandatory in all cases.
II	Category II denotes diseases for which TA is accepted as second-line treatment, either as a standalone treatment or in conjunction with other treatments.
III	Category III diseases are those for which the optimum role of TA is not established and treatment decisions on an individual basis are recommended.
IV	Category IV indicates disorders for which published evidence suggests or demonstrates that TA is ineffective or harmful.

Following are the indications for therapeutic apheresis and the ASFA category recommendations for 2007, 2010, and 2013. (Note: NC: Not Categorized)

Disease Group / Name / Condition	2007	2010	2013
Autoimmune			
Catastrophic antiphospholipid syndrome	III	II	II
Cryoglobulinemia	I	I	I
Pemphigus vulgaris	III	IV	III
Systemic lupus erythematosus			
Manifestations other than nephritis	III	NC	NC
Severe	NC	II	II
Nephritis	IV	IV	IV
Hematologic			
ABO incompatible hematopoietic			
progenitor cell transplantation	II	II	II

Aplastic anemia	III	III	III
Pure red blood cell aplasia	III	II	III
Autoimmune hemolytic anemia:			
warm autoimmune hemolytic anemia	III	III	III
cold agglutinin disease	III	II	II
Coagulation factor inhibitors	III	IV	IV
Hyperviscosity in monoclonal gammopathies	I	I	I
Idiopathic thrombocytopenic purpura	I	I	NC
Refractory immunoadsorption	II	NC	NC
Refractory or non-refractory	IV	NC	NC
Myeloma and acute renal failure (in 2010 and 2013 III II II Myeloma cast nephropathy)	III	II	II
Post-transfusion purpura	III	III	III
Red blood cell alloimmunization in pregnancy	II	II	III
Thrombotic thrombocytopenic purpura	I	I	I
Metabolic			
Acute liver failure	III	III	III
Sepsis (in 2010 and 2013, with multiorgan failure)	III	III	III
Thyrotoxicosis (in 2010 and 2013, thyroid storm)	III	III	III
Neurological			
Acute disseminated encephalomyelitis	III	II	II
Acute inflammatory demyelinating polyneuropathy			
(Guillain-Barré syndrome)	I	I	I
Acute inflammatory demyelinating polyneuropathy,	NC	NC	III
Post IVIG			
Chronic inflammatory demyelinating			
polyradiculoneuropathy	I	I	I
Lambert-Eaton myasthenic syndrome	II	II	II
Multiple sclerosis			
Acute CNS inflammatory demyelinating disease	II	II	II
Devic’s syndrome	III	NC	NC
Chronic progressive	III	III	III
Myasthenia gravis	I	I	
In 2013, moderate-severe			I
In 2013, Pre-thymectomy			I
Paraneoplastic neurologic syndromes	III	III	III
Paraproteinemic polyneuropathies			
IgG/IgA	I	I	I
IgM	II	I	I

Multiple myeloma	III	III	III
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections;			
Sydenham's chorea (SC)			
PANDAS (2007, severe)	I	I	I
SC (2007 severe)	I	I	I
Rasmussen's encephalitis	II	NC	III
Stiff-person syndrome	III	IV	III
Renal			
ANCA-associated rapidly progressive glomerulonephritis (Wegener's granulomatosis) II			
Dialysis dependence	NC	I	I
Dialysis independence	NC	III	III
Anti-glomerular basement membrane disease			
(Goodpasture's syndrome)	I		
Diffuse alveolar hemorrhage (DAH)	NC	I	I
Dialysis dependence and no DAH	NC	IV	III
Dialysis independence	NC	I	I
Focal segmental glomerulosclerosis			
Primary	III	NC	NC
Secondary	III	NC	NC
Recurrent	NC	I	I
Hemolytic uremic syndrome (HUS); thrombotic microangiopathy; transplant associated microangiopathy			
Idiopathic HUS	III	III	NC
Transplant-associated microangiopathy	III	NC	NC
Diarrhea associated pediatric	IV	NC	NC
Atypical HUS due to complement factor	NC	II	II
gene mutations			
Atypical HUS due to autoantibody to factor H	NC	I	I
Diarrhea associated HUS or typical	HUS	NC	IV
In 2013, Shiga toxin-associated			IV
S. pneumonae associated			III
Renal transplantation: antibody mediated rejection; HLA desensitization			
Antibody mediated rejection	II	I	I
LA desensitization	II	NC	
Desensitization, living donor, positiv	e NC	II	I
crossmatch due to donor-specific HLA antibody			
High PRA: cadaveric donor	NC	III	III
Rheumatic			

Scleroderma (progressive systemic sclerosis)	III	III	III
Transplantation			
ABO incompatible solid organ transplantation			
Kidney	II	II	
In 2013, densentization, living-donor			I
humeral rejection			II
Heart (infants)	II	II	NC
Liver (2010 perioperative)	III	III	
In 2013, desensitization living-donor			I
desensitization, deceased-donor			II
humeral rejection			III
Heart transplant rejection			
Treatment	III	NC	NC

Medicare National Coverage

The Centers for Medicare and Medicaid Services, Medicare Coverage Database, National Coverage Determination for apheresis (therapeutic pheresis)(48) states:

“For purposes of Medicare coverage, apheresis is defined as an autologous procedure, i.e., blood is taken from the patient, processed, and returned to the patient as part of a continuous procedure (as distinguished from the procedure in which a patient donates blood preoperatively and is transfused with the donated blood at a later date). Apheresis is covered for the following indications: Plasma exchange for acquired myasthenia gravis; Leukapheresis in the treatment of leukemia; Plasmapheresis in the treatment of primary macroglobulinemia (Waldenström); Treatment of hyperglobulinemias, including (but not limited to) multiple myelomas, cryoglobulinemia and hyperviscosity syndromes; Plasmapheresis or plasma exchange as a last resort treatment of thrombotic 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 pruritus 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.”

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Billing Coding/Physician Documentation Information

36514 Therapeutic apheresis; for plasma pheresis
36515 Therapeutic apheresis; with extracorporeal immunoadsorption and plasma reinfusion
36516 Therapeutic apheresis; with extracorporeal selective adsorption or selective filtration and plasma reinfusion
S2120 Low density lipoprotein (LDL) apheresis using heparin-induced extracorporeal LDL

precipitation

In 2003, CPT introduced a variety of CPT codes that describe different types of apheresis procedures. CPT codes 36514 specifically describe “therapeutic apheresis, for plasmapheresis.”

Policy Implementation/Update Information

10/1/88	New policy titled *Therapeutic Apheresis* added to the Surgery section.
9/1/00	No policy statement changes.
9/1/01	No policy statement changes.
9/1/02	Title of policy changed to *Plasma Exchange / Plasmapheresis*. Policy statement revised to include Hemolytic uremic syndrome (HUS); IgA or IgG paraproteinemia polyneuropathy; HELLP syndrome of pregnancy and post-transfusion purpura as medically necessary.
9/1/03	No policy statement changes.
9/1/04	No policy statement changes.
9/1/05	No policy statement changes.
9/1/06	Policy statement revised with addition of policy statements and discussion of plasmapheresis in the setting of solid organ transplantation, considered medically necessary. References 21-30 added.
9/1/07	No policy statement changes.
9/1/08	No policy statement changes.
9/1/09	No policy statement changes.
6/1/10	The policy statement has been modified to include: Guillain-Barré syndrome severity grades 1-2 as medically necessary; use in the pediatric population is investigational for mild and moderate forms of GBS and medically necessary for the severe form of GBS; the policy statement has been modified to include severe manifestations of mixed cryoglobulinemia (MC) as medically necessary when used in combination with immunosuppressive therapy; typical- hemolytic uremic syndrome is investigational (considered medically necessary in previous updates) and investigational for treatment of PANDAS, Sydenham chorea, Refsum’s disease, cryoglobulinemia (except severe MC), myasthenia gravis with anti-MuSk antibodies; additional conditions were added as investigational based on American Society for Apheresis (ASFA) review. Title changed from “Plasma Exchange (Plasmapheresis) to “Plasma Exchange.”
9/1/10	No policy statement changes.
9/1/11	Added “post-transfusion purpura” back into the medically necessary policy statement as it was mistakenly dropped in the last reorganization of the statements. The Guillain-Barré syndrome disability scale was added to the appendix.
9/1/12	Myeloma with acute renal failure and catastrophic antiphospholipid syndrome were changed to medically necessary. Dense deposit disease with Factor H deficiency and/or elevated C3 nephritis factor and focal segmental glomerulosclerosis after renal transplant were added as medically necessary. The investigational statement on focal segmental glomerulosclerosis was modified to indicate that it applied to situations other than after renal transplant. Hyperviscoscity syndromes with renal failure (other than associated with multiple myeloma or Waldenstrom’s macroglobulinermia) added as investigational. In addition, the serum creatinine threshold was removed from the policy statement on ANCA-associated vasculitis.
9/1/13	No policy statement changes.
9/1/14	Minor changes to bullet points on multiple sclerosis for clarity only. No policy statement changes.

Appendix

Diagnostic Criteria for Diagnosis of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

The following criteria are adapted from the Task Force Report of the Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force. (Neurology 1991; 41:617-18) The report included mandatory, supportive, and exclusionary diagnostic criteria. Only the mandatory criteria are excerpted

here. The criteria are based on a combination of clinical observations, physiologic studies, pathologic features (i.e., nerve biopsy), and studies of the cerebrospinal fluid (CSF).

I. Clinical
Mandatory
1. Progressive or relapsing motor and sensory, rarely only motor or sensory, dysfunction of more than 1 limb or a peripheral nerve nature, developing over at least 2 months.
2. Hypo- or areflexia. This will usually involve all 4 limbs.

II. Physiologic Studies
Mandatory
Nerve conduction studies including studies of proximal nerve segments in which the predominant process is demyelination.

Must have 3 of 4:
1. Reduction in conduction velocity (CV) in 2 or more motor nerves:
    a. <80% of lower limit of normal (LLN) is amplitude >80% of LLN
    b. <70% of LLN is amplitude <80% of LLN

2. Partial conduction block or abnormal temporal dispersion in 1 or more motor nerves: either peroneal nerve between ankle and below fibular head, median nerve between wrist and elbow, or ulnar nerve between wrist and below elbow.

    Criteria suggestive of partial conduction block: <15% change in duration between proximal and distal sites and >20% drop in negative peak (p) area or peak to peak (p-p) amplitude between proximal and distal sites.

    Criteria for abnormal temporal dispersion and possible conduction block: >15% change in duration between proximal and distal sites and >20% drop in p area or p-p amplitude between proximal and distal sites and >20% drop in p or p-p amplitude between proximal and distal sites. These criteria are only suggestive of partial conduction block as they are derived from studies of normal individuals. Additional studies, such as stimulation across short segments or recording of individual motor unit potentials, are required for confirmation.

3. Prolonged distal latencies in 2 or more nerves:
    a. >125% of upper limit of normal (LEN) is amplitude >80% of LLN
    b. >150% of LEN if amplitude <80% of LLN.

4. Absent F waves or prolonged minimum
    a. >120% of ULN if amplitude >80% of LLN
    b. >150% of ULN if amplitude <80% of LLN.

III. Pathologic Features
Mandatory
Nerve biopsy showing unequivocal evidence of demyelination and remyelination.

Demyelination by either electron microscopy (>5 fibers) or teased fiber studies >12% of 50 fibers, minimum of 4 internodes each, demonstrating demyelination/remyelination.

IV. CSF Studies
Mandatory
1. Cell count <10/mm-3 if HIV-seronegative or <50/mm-3 is HIV seropositive
2. Negative VDRL

The following is the disability scale as first described by Hughes et al. in Lancet 1978; 2(8093):750-3

0. Healthy
1. Minor symptoms or signs of neuropathy but capable of manual work
2. Able to walk without support of a stick but incapable of manual work
3. Able to walk with a stick, appliance or support
4. Confined to bed or chair bound
5. Requiring assisted ventilation
6. Dead

The scale has been modified since 1978 and appears below as it did in the Hughes et al. 2007 systematic review published in Brain 2007; 130(9):2245-57.

0. Healthy
1. Minor symptoms or signs of neuropathy but capable of manual work*/capable of running*
2. Able to walk without support of a stick *(5 m across an open space)* but incapable of manual work*/running*
3. Able to walk with a stick, appliance or support *(5 m across an open space)*
4. Confined to bed or chair bound
5. Requiring assisted ventilation *(for any part of the day or night)*
6. Death
