**Special Article**

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# Assessment of plasmapheresis

Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology



In this article, we have assessed the value of plasmapheresis as a tool for treatment of patients with neurologic disorders. We chose to use the more common term "plasmapheresis," which technically means removal of plasma only, for the proper term, "plasma exchange," which technically refers to both removal of plasma and its replacement. In the literature, these terms are used interchangeably.

Using the Medline search, including the "back 90" and "back 85" backfiles, we batched the terms "plasmapheresis" and "neurologic disease (exploded)" from 1985 to 1995, which yielded a total of 544 articles. The titles of these articles were scanned and those thought relevant to the assessment were reviewed in their entirety. In addition, a Medline search was made that cross-referenced the terms "plasmapheresis" and "neurologic diseases (exploded)" with "randomized controlled trial" (publication type). We excluded articles about plasmapheresis used to treat stroke. This led to only six citations. We also relied upon the NIH Consensus Conference of 1986 on Plasmapheresis and Neurologic Disease.[1] We spoke with experts in the field, and several individuals wrote directly to the AAN to express their opinions.

**Plasmapheresis.** *Mechanics.* Plasmapheresis (PP) is the removal of whole blood from the patient, its separation by machine into component parts, and then the return of certain of those components to the patient. The PP described in this assessment is the separation of the formed elements from the liquid elements in blood, the reconstitution of the formed elements with another plasma source (either natural or artificial), and the reinfusion of that plasma source along with the patient's own formed elements. On occasion, although rarely used in neurologic disorders, this procedure can be adjusted to remove white cells, platelets, or immunoglobulins alone.

The literature refers to both discontinuous- and continuous-flow machines. In *discontinuous-flow machines*—the older and now less common type—whole blood is removed from the patient, separated and reconstituted, and then the removal of whole blood stopped and the patient reinfused with the reconstituted solution; that is, either blood goes out or the reconstitute goes in, but both do not occur simultaneously. The newer and more efficient *continuous-flow machines* remove whole blood from one intravenous site while simultaneously and continuously returning the reconstituted elements through another intravenous site. Continuous-flow machines shorten the time of PP. If venous access is limited, most continuous-flow machines can be operated in a discontinuous manner with one venous access.

Replacement solutions. Usually 1 to 1½ plasma volumes are removed at each procedure. This requires replacement with albumin or plasma protein fractions in combination with sterile saline. There is no risk of disease transmission if blood products other than albumin and plasma protein fractions are avoided.

Anticoagulants. Regional anticoagulation with citrate is usually used. While this may result in transient hypocalcemia, it is less risky than using systemic anticoagulation with heparin.

*Presumed mechanisms.* A variety of possible mechanisms for the actions of therapeutic PP has been proposed, including removal of antibody, removal of alloantibody, removal of immune complexes, removal of a monoclonal protein, removal of toxin or cytokine(s), replenishment of a specific plasma factor, and, lastly, the placebo effect. For most neurologic diseases, PP presumably removes pathogenic antibodies from the immunoglobulin fraction of serum. Only in myasthenia gravis (MG), however, has this presumption been shown,[2,3] in that patient improvement is associated with a drop in antibody titers as a result of PP. In most of the other diseases discussed below, the pathogenic antibodies are not identified or, if identified, have not been measured in a rigorous fashion. It should be noted, however, that other mechanisms may exist. Indeed, PP can be looked upon as a "blunderbuss" that removes all the nonformed elements in plasma, including immunoglobulins, cytokines, and other serum factors, in a nonspecific fashion. The specific factor whose removal is crucial in therapeutically successful PP is thus not specifically known. Surprisingly, systematic data on the effects of PP in controls are scarce; that is, little is known about the effects of PP

See page 842 for Panel and Subcommittee members.

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***Table*** *Summary of the American Academy of Neurology assessment of plasmapheresis*

| Disease | Definitions | Quality | Strength |
|---|---|---|---|
| Guillain-Barré syndrome—severe | Established | Class I | Type A |
| Chronic inflammatory demyelinating polyneuropathy | Established | Class I | Type A |
| Polyneuropathy with monoclonal gammopathies of undetermined significance: | | | |
| IgG/IgA | Established | Class I | Type A |
| IgM | Investigational | Class I | |
| Myasthenia gravis—Pre-op preparation and crisis | Established | Class III | Type C |
| Lambert-Eaton myasthenic syndrome | Possibly useful | Class II/III | |
| Refsum's disease | Investigational | Class III | |
| Acquired neuromyotonia | Investigational | Class III | |
| Stiff-man syndrome | Investigational | Class III | |
| Cryoglobulinemic polyneuropathy | Investigational | Class III | |
| Central nervous system systemic lupus | Investigational | Class III | |
| Acute disseminated encephalomyelitis | Investigational | Class III | |
| Multiple sclerosis | Possibly useful | Class I/II | |

on serum levels of the variety of factors now known to be important in immune reactions.

*Cost.* The cost of PP varies considerably, typically $1,000 to $2,000 per procedure. Thus, a five-session course of PP can cost between $5,000 and $10,000.

*Safety profile.* In experienced hands, PP is extremely safe. Although hypotension, dizziness, and perioral tingling (hypocalcemia) may occur either during or following PP, most of these reactions are rapidly recognized and reversed, and are rarely serious.[4] There is a risk of infection from the intravenous manipulations, but this has proven to be minimal. Probably the greatest risk to patients are the procedures necessary to ensure adequate venous access, in particular the placement of the central venous catheters, which are associated with a low but definite risk of pneumothorax, thrombosis, and infection. Deaths from PP have been reported, but have generally been related to preexisting illness.

**Diseases.** *Guillain-Barré syndrome.* Three randomized controlled trials[5-7] have shown that PP improves the outcome of patients with severe Guillain-Barré syndrome (GBS). In these studies, entry was limited to those patients with GBS severe enough to prevent independent walking. PP is considered *established* for this population with severe GBS, based on *Class I* evidence and a *Type A* recommendation. Whether PP should be used in patients with GBS who are less severely affected is unknown at this time.

*Chronic inflammatory demyelinating polyradiculoneuropathy.* A randomized controlled trial performed by Dyck et al.[8] showed that a significant proportion of patients with chronic inflammatory demyelinating polyneuropathy improved following PP. Thus, PP is a useful modality of therapy in this group of patients, who may also benefit from oral prednisone and intravenous human immune globulin, as shown in randomized controlled trials.[9-11] Which of these therapies is best will depend on a number of factors, as has been reviewed recently.[10] PP is considered *established* for this disorder, with minimal *Class I* evidence and a *Type A* recommendation.

*Polyneuropathy associated with monoclonal gammopathies of undetermined significance.* A randomized controlled trial[10] has shown that patients with polyneuropathy associated with IgA and IgG monoclonal gammopathies of undetermined significance (MGUS) improve following therapy with PP. Those with IgM MGUS and polyneuropathy did not improve. The patients entering this study were heterogeneous and included those with both demyelinating and axonal polyneuropathies. Patients in the IgM MGUS group may have included those with anti-myelin-associated glycoprotein antibodies. Because of continuing controversy concerning the exact relationship of the monoclonal protein to the neuropathy, treatment decisions in these patients remain individualized. PP may be considered *possibly useful* for these disorders. For those with IgA and IgG, *Class I* evidence would indicate that PP is *established.*

*Myasthenia gravis.* Although no controlled clinical trials have been performed of PP in MG, a sufficient number of case series, as well as the experiences of experts, have been reported[1,2,12,13] to establish clearly the value of PP in MG. The two most common indications for PP in myasthenia are preoperative preparation and treatment of myasthenic crisis. PP would be considered *established* for MG for these indications, based on *Class III* evidence, *Type C.* PP may occasionally be used in the chronic long-term therapy of patients with myasthenia,[14] although most authorities prefer immunosuppressant drugs.[15]

*Lambert-Eaton myasthenic syndrome.* While no controlled trials exist on the use of PP in the Lambert-Eaton myasthenic syndrome (LEMS), a case series[16] has suggested a benefit. The rationale is similar to that in myasthenia; that is, patient strength should be improved by the removal of the pathogenic antibody to the voltage-gated calcium channel. In most cases, patients are treated long-term with a combination of corticosteroids and immunosuppressant drugs.[17] PP would be considered *promising* for LEMS based on *Class II and III* evidence, *Type C.*

*Multiple sclerosis.* Khatri et al.[18] studied 54 patients with chronic-progressive multiple sclerosis (MS) who, in addition to receiving oral low-dose cyclophosphamide and prednisone, were randomized to receive either true PP or sham PP for 20 weeks. This study showed that patients in the true-PP arm were more likely to improve (14/26 at 5 months and 11/26 at 12 months) than were those in the sham-PP arm (8/29 at 5 months and 5/29 at 11 months).

Weiner et al.[19] studied 116 patients with acute exacerbations of MS randomized to receive either PP or sham PP,

both in association with ongoing ACTH and oral cyclophosphamide, for 24 months. No overall differences emerged among these patients, even when analyzing for subtypes of MS, such as relapsing-remitting or chronic-progressive.

The Canadian Cooperative Multiple Sclerosis Study Group[20] compared four treatments in patients with progressive MS: (1) intravenous cyclophosphamide and oral prednisone, (2) daily oral cyclophosphamide and alternate-day prednisone, (3) weekly PP, or (4) placebo medication and sham PP. All patients were followed for at least 12 months, with a mean of 30 months, and no differences were found among the groups in the primary analysis of rates of treatment failure. Additionally, no differences were detected in the proportions of patients who improved among the groups during the course of this study. In the study[18] showing an improvement in the true- vs sham-PP patients, all patients were on concomitant immunosuppressant drug therapy. In the only study in which PP was compared to sham PP and to immunosuppressant drug therapy, no clear benefit was shown for PP alone.

A recent report by Rodriguez et al.[21] suggests that in certain individuals with acute fulminant MS, PP may be of benefit, without the use of concomitant immunosuppressive therapy. The exact role of PP in the care and treatment of patients with multiple sclerosis remains unclear. While selected MS patients may benefit from this therapy, they are also likely to be on concomitant immunosuppressant drug treatments, so that the true effect of PP is difficult to determine. Therapeutic PP may have a role in selected cases of fulminant MS, and a double-blind NIH-funded trial is currently under way. Based on these studies, PP for the treatment of MS must be considered *promising*, based on some *Class I* evidence.

*Miscellaneous disorders.* PP may have a role in *Refsum's disease* in lowering the levels of phytanic acid,[22] but the exact role of PP in relationship to dietary restriction of phytanic acid remains to be elucidated. Single reports have suggested that PP may be of use in *acute disseminated encephalomyelitis*,[23] in *acquired neuromyotonia*,[24] in *stiff-man syndrome*,[25] and in *central nervous system systemic lupus*.[26] In addition, multiple case series[27-32] have suggested that PP may be of use in *cryoglobulinemic polyneuropathy*. The use of PP in Refsum's disease, acute disseminated encephalomyelitis, acquired neuromyotonia, stiff-man syndrome, central nervous system systemic lupus, and cryoglobulinemic polyneuropathy, must be considered *investigational*, based on *Class III* evidence.

*Amyotrophic lateral sclerosis.* No evidence suggests that PP has any role in the treatment of patients with amyotrophic lateral sclerosis (Consensus Conference, 1986).

*Paraneoplastic neurologic syndromes with circulating antibodies.* Based on the case series by Graus et al.,[33] no evidence suggests that PP has a role in treating patients with neurologic paraneoplastic syndromes with circulating autoantibodies.

**Summary.** Based on the review of the literature, therapeutic PP has a definite role in the treatment of patients with GBS, CIDP, polyneuropathies associated with MGUS, MG, and LEMS (table). PP may have a role in treating patients with Refsum's disease, acquired neuromyotonia, stiff-man syndrome, cryoglobulinemic polyneuropathy, CNS-SLE, ADEM, and MS, but these decisions should be made on a case-by-case basis. PP has no role in treating patients with ALS or paraneoplastic syndromes with circulating autoantibodies.


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**Definitions**

**Safety:**
A judgment of the acceptability of risk in a specified situation; e.g., for a given medical problem, by a provider with specified training, at a specified type of facility.

**Effectiveness:**
Producing a desired effect under conditions of actual use.

**Established:**
Accepted as appropriate by the practicing medical community for the given indication in the specified patient population.

**Possibly useful:**
Given current knowledge, this technology appears to be appropriate for the given indication in the specified patient population. As more experience and long-term follow-up are accumulated, this interim rating will change.

**Investigational:**
Evidence insufficient to determine appropriateness, warrants further study. Use of this technology for given indication in the specified patient population should be confined largely to research protocols.

**Doubtful:**
Given current knowledge, this technology appears to be inappropriate for the given indication in the specified patient population. As more experience and long-term

follow-up are accumulated, this interim rating will change.

**Unacceptable:**

Regarded by the practicing medical community as inappropriate for the given indication in the specified patient population.

**Suggested Quality of Evidence Ratings:**

**Class I:**

Evidence provided by one or more well-designed, randomized, controlled, clinical trials.

**Class II:**

Evidence provided by one or more well-designed clinical studies such as case control, cohort studies, etc.

**Class III:**

Evidence provided by expert opinion, nonrandomized historical controls, or case reports of one or more.

**Suggested Strength of Recommendations Ratings:**

**Type A:**

Strong positive recommendation, based on Class I evidence, or, when circumstances preclude randomized clinical trials, overwhelming Class II evidence.

**Type B:**

Positive recommendation, based on Class II evidence.

**Type C:**

Positive recommendation, based on strong consensus of Class III evidence.

**Type D:**

Negative recommendation, based on inconclusive or conflicting Class II evidence.

**Type E:**

Negative recommendation, based on evidence of ineffectiveness or lack of efficacy, based on Class II or Class I evidence.



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