

Therapeutic Plasma Exchange: An Update from the Canadian Apheresis Group

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In 1997, the Canadian Apheresis Group reviewed data on 103 416 plasma exchange procedures that had been collected since 1980. Although the number of plasma exchanges gradually increased (from 3189 to 8208 per year), the pattern changed. In 1981, the five most frequent indications for plasma exchange resulted in 55% of all such procedures; by 1997, the five most frequent indications for plasma exchange resulted in 81.1% of all such procedures. During this period, three conditions that were originally among the most frequent indications for plasma exchange became among the least frequent. This paper reviews the published evidence that supports or refutes the use of plasma exchange in the category of the five most frequent indications from 1981 to 1997: thrombotic thrombocytopenic purpura, myasthenia gravis, chronic inflammatory demyelinating polyneuropathy, Waldenström macroglobulinemia, the Guillain-Barré syndrome, rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis. For most disorders, use of plasma exchange procedures is correlated with published evidence, and the changing patterns of plasma exchange use by members of the Canadian Apheresis Group reflect published evidence. Annual center-by-center reviews of use of plasma exchange may also have influenced practice patterns.

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*For members of the Canadian Apheresis Group, see Appendix.

The Canadian Apheresis Group (CAG) was formed in 1980 under the auspices of National Health and Welfare, Canada. The group includes representatives from 42 apheresis units in the 19 major medical centers in Canada. During the past 18 years, the CAG has been involved in the organization and direction of several randomized, controlled studies of plasma exchange (1-5). In addition, the CAG has acted as a registry by collecting and annually reviewing information on all 103 416 apheresis procedures (from 1980 to 1997) with the directors of each medical center. Although the annual meeting of the CAG medical directors focuses on new evidence and techniques for plasma exchange, an annual center-by-center review has been a standard feature. In these reviews, the directors of each medical center are asked to explain variances in their center's activity with reference to available published evidence and to address the feasibility of creating a future pilot or randomized, controlled study.

From 1980 to 1981, members of the CAG performed 3189 plasma exchanges for 70 conditions. In 1997, more than 8208 plasma exchanges were done for 23 conditions. In 1981, the five most frequent indications for plasma exchange represented 55% of all such procedures; by 1997, the percentage was 81.1% (Table 1). Although four of the five conditions that most frequently indicated plasma exchange in 1981 were also among the five conditions that most frequently indicated plasma exchange in 1997, the rank of the conditions and the number of plasma exchanges performed have changed substantially (Table 1, Figures 1 and 2). Systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis were once among the disorders that most frequently resulted in plasma exchange; from 1980 to 1997, they became the disorders that most infrequently resulted in plasma exchange (Figure 2). Because of this changing pattern in the use of therapeutic plasma exchange by members of the CAG, the advisory board requested that each member provide the published evidence that supported or refuted the use of plasma exchange for the most frequently treated disorders recorded in the CAG registry.

Literature Review Methods

The evidence was critically reviewed by the CAG board, and the information was augmented by a computerized MEDLINE search of the English-language literature published from 1983 to the present. At least one of the authors reviewed all publications, and further references were sought from all members of the CAG. All randomized, controlled trials and the only available meta-analysis were reviewed and given higher priority. However, controlled retrospective cohort studies and mechanistic, historical, anecdotal reports were also evaluated. This update is a result of efforts to assess the available published evidence and correlate it with the changing patterns of practice noted by the CAG in the use of plasma exchange from 1981 to 1997.

Thrombotic Thrombocytopenic Purpura

As noted in Table 1 and Figure 1, the percentage of plasma exchanges has quadrupled and the num-

Table 1. Comparison of Use of Plasma Exchange in 1981 and 1997 for the Five Most Frequent Indications

Diagnosis	1981		1997	
	Patients	Plasma Exchange Procedures Performed*	Patients	Plasma Exchange Procedures Performed*
	<i>n</i>	<i>n</i> (%)	<i>n</i>	<i>n</i> (%)
Myasthenia gravis	64	683 (21.4)	144	1179 (14.4)
Systemic lupus erythematosus	56	342 (10.7)		
Thrombotic thrombocytopenic purpura	30	276 (8.7)	206	3182 (38.8)
The Guillain-Barré syndrome (acute cases)	39	264 (8.3)	82	542 (6.2)
Waldenström microglobulinemia	40	198 (5.9)	80	610 (7.4)
Chronic inflammatory demyelinating polyneuropathy			95	1171 (14.3)
Total	229	1763 (55)	607	6684 (81.1)

* Numbers in parentheses represent the percentage of the total number of plasma exchange procedures performed during the year.

ber of patients treated for thrombotic thrombocytopenic purpura from 1981 to 1997 has increased sevenfold. In 1925, Eli Moschowitz published a report titled “An acute febrile pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries: an undescribed disease” (23). In a presentation of this report, Moschowitz said, “I have learned that Dr. Max Lederer of Brooklyn has seen four cases clinically identical with the one described in this report. He permits me to state that, thus far, no cause has been found, and that all four patients recovered promptly after a single transfusion of blood” (23). This observation was not used in clinical practice until 1959, when Rubenstein and coworkers (24) reported an unusual remission in a patient with thrombotic thrombocytopenic purpura after fresh blood-exchange transfusion. A later report by Bukowski and colleagues (25)—in which two patients responded to exchange transfusion and plasma exchange with fresh frozen plasma—and a 1977 single case report by Byrnes and Khurana (26) generated enthusiasm for the use of plasma and plasma exchange in the treatment of thrombotic thrombocytopenic purpura.

Byrnes and Khurana (26) were initially using exchange transfusion to remove a toxic substance. However, the exchange transfusion, which was performed with washed red cells and albumin instead of whole blood, had no effect. This suggested that remission might be induced by the replacement of a missing plasma factor, an idea corroborated by the patient’s immediate response to whole-plasma infusion and subsequent ongoing requirement for plasma. This dramatic series of observations of the role of plasma, coupled with Bukowski and colleagues’ findings on plasmapheresis (26), led to the widespread use of both plasma infusion and plasma exchange for individual cases of thrombotic thrombocytopenic purpura. In 1991, a controlled prospective study that compared plasma exchange with plasma infusion in patients with thrombotic thrombocytopenic purpura reported a statistically significant benefit for plasma exchange (1). One hundred

two patients with thrombotic thrombocytopenic purpura were randomly assigned to receive plasma exchange or plasma infusion with fresh frozen plasma on 7 of the first 9 days after study entry (Table 2). Researchers concluded that plasma exchange was more effective than plasma infusion in the treatment of thrombotic thrombocytopenic purpura. An earlier report of a randomized, controlled study of 30 patients had shown a nonstatistical benefit for plasma exchange compared with plasma infusion (6). However, in 1991, a stepwise increase in the number of patients undergoing plasma exchange for thrombotic thrombocytopenic purpura was noted, coincident with the CAG publication (Figure 1).

Bell and coworkers (27) strengthened the conclusions of the CAG study (1) and helped to establish plasma exchange as the mainstay of therapy for thrombotic thrombocytopenic purpura. In their study of 78 patients with complicated thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome, only 8 patients who received plasma exchange died. Byrnes and colleagues (28) later reported on 7 patients who did not respond to plasma exchange with fresh frozen plasma but responded to plasma exchange with cryosupernatant (in which the largest von Willebrand factor multimers are removed). A CAG report (29) on the use of cryosupernatant plasma in 18 patients with resistant thrombotic thrombocytopenic purpura and 40 patients with recent-onset thrombotic thrombocytopenic purpura extended this observation. Sixty-one percent of patients who were resistant to fresh frozen plasma responded to cryosupernatant exchange in 7 days, and 83% survived for 1 month. Seventy-five percent of the previously untreated patients responded to cryosupernatant exchange in 7 days, and the 1-month survival rate was 95%. These results are more favorable than those noted in the 1991 plasma exchange report, in which researchers used fresh frozen plasma (1). Two recent reports (30, 31) provide a mechanistic explanation for these results. A transient relative deficiency of von Willebrand factor-cleaving protease in patients with

thrombotic thrombocytopenic purpura is caused by antibodies that probably have a pathogenic role in widespread platelet thrombosis. At low titers, this antibody inhibitor would potentially respond to simple plasma infusion, which replaces the relatively deficient protease. At high levels, however, this antibody inhibitor would require removal of the inhibitor and replacement of the protease by plasma exchange. The results might be expected to be superior if the replacement solution not only had protease but was deficient in von Willebrand factor multimers, as is cryosupernatant. These recent reports (30, 31) provide a mechanism for the established study evidence that plasma exchange is an effective form of therapy for thrombotic thrombocytopenic purpura and that cryosupernatant is at least as effective as and perhaps more effective than plasma as a replacement solution for patients with thrombotic thrombocytopenic purpura.

Myasthenia Gravis

Myasthenia gravis was the second most common indication for plasma exchange in 1997. Plasma exchange therapy was first described as a form of

treatment in 1976 by Pinching and Peters (32). Three patients with myasthenia gravis did not respond to anticholinesterases, thymectomy, or steroids; in the two acquired cases of myasthenia gravis, plasma exchange was associated with unequivocal improvement in muscle weakness and fatigue, suggesting that a humoral factor in the plasma was causing the disorder of neuromuscular transmission. This study was followed by two more detailed studies (33, 34) that demonstrated a close correlation with clinical functional improvement and a reduction in acetylcholine receptor antibody levels. A 1998 review from a National Institutes of Health Consensus Development Conference (7) concluded that plasma exchange was useful in strengthening patients with myasthenia gravis before thymectomy and early in the postoperative period and that it could decrease the occurrence of symptoms during the initiation of immunosuppressive drug therapy in an acute crisis.

Although a controlled trial of plasma exchange in patients with myasthenia gravis has not been performed, one trial (8) compared plasma exchange with high-dose intravenous immunoglobulin in patients with myasthenia gravis (Table 2). Although the trial showed no pronounced differences in the

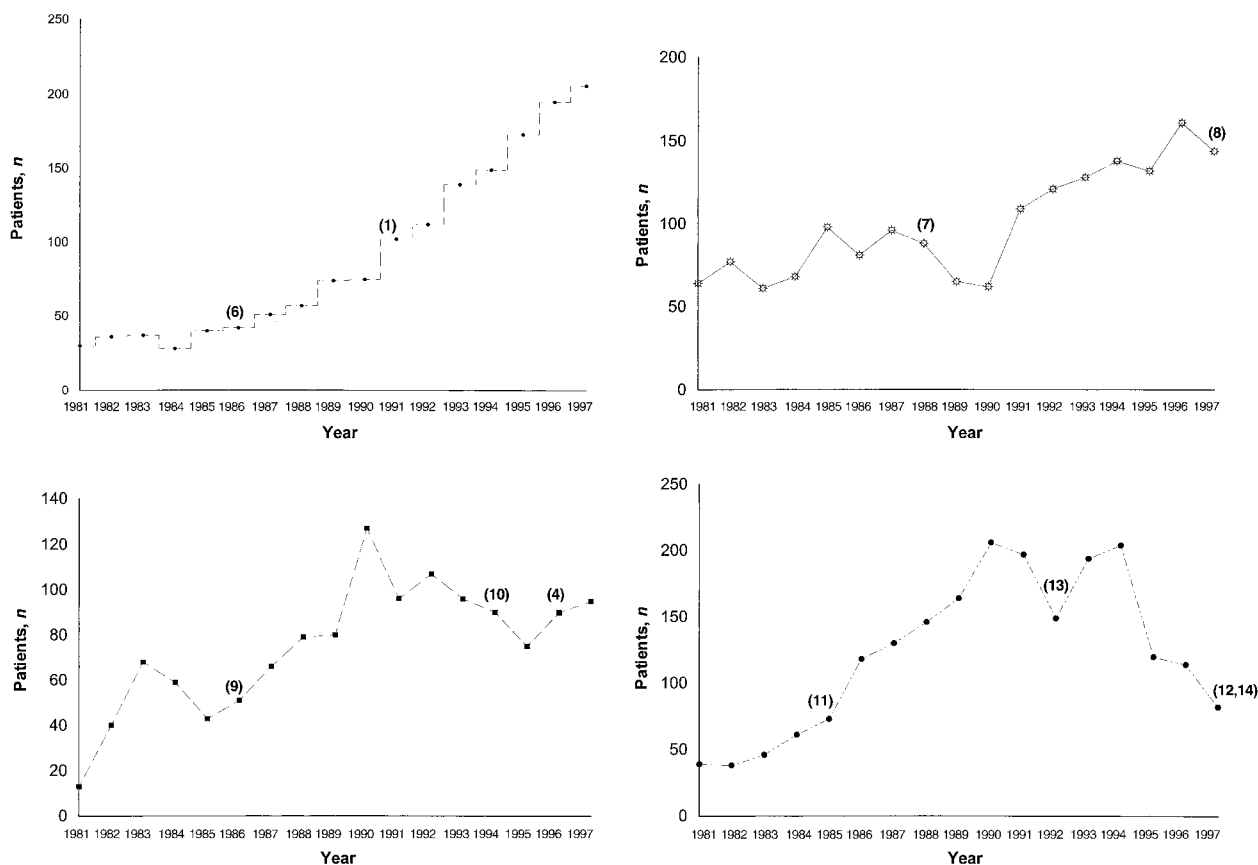


Figure 1. Changing trends in use of plasma exchange by members of the Canadian Apheresis Group (from 1981 to 1997) in patients with thrombotic thrombocytopenic purpura (top left), myasthenia gravis (top right), chronic inflammatory demyelinating polyneuropathy (bottom left), and acute cases of the Guillain-Barré syndrome (bottom right). Numbers in parentheses are reference numbers.

efficacy of the treatments, it established intravenous immunoglobulin as a potential therapeutic alternative in acute phases of myasthenia gravis. This recent finding may have been responsible for reversing the gradual increase in the number of cases of myasthenia gravis treated with plasma exchange since 1981 (Figure 1).

Chronic Inflammatory Demyelinating Polyneuropathy

In 1997, the third most common indication for plasma exchange was chronic inflammatory demyelinating polyneuropathy. In 1979, early case reports indicated favorable responses to therapeutic plasma exchange in selected patients with chronic inflammatory demyelinating polyneuropathy (35). The finding that serum samples from patients with this condition cause demyelination or functional peripheral nerve deficit provided a rationale for the use of plasma exchange. This response was tested in several small groups of patients, and the observations were derived from nonblinded assessments that were subject to bias. Use of plasma exchange for the treatment of chronic inflammatory demyelinating polyneuropathy initially increased and decreased but in 1986 saw a surge in activity (followed with

some variation) that lasted until 1994 (Figure 1). In 1986, Dyck and coworkers (9) reported that in a randomized, double-blind, sham apheresis study of 29 patients with chronic inflammatory demyelinating polyneuropathy, a subset of patients seemed to benefit from plasma exchange (Table 2). However, patients who had plasma exchange received varying courses of immunosuppressive drugs, and it was difficult to eliminate this bias.

Ten years later, a double-blind, sham apheresis, controlled crossover trial of plasma exchange in patients with chronic inflammatory demyelinating polyneuropathy was reported (4) (Table 2). Plasma exchange was associated with substantial improvement in all clinical outcome measures. Follow-up again described rebound phenomena with rapid deterioration, which led the authors to conclude that although a favorable, often remarkable, response can be expected in most patients with chronic inflammatory demyelinating polyneuropathy, long-term immunosuppressive treatment is often needed.

In 1994, a small study by Dyck and colleagues (10) at the Mayo Clinic compared plasma exchange with immunoglobulin infusion in patients with chronic inflammatory demyelinating polyneuropathy (Table 2). The change in the end points was a large and clinically significant improvement, and the open

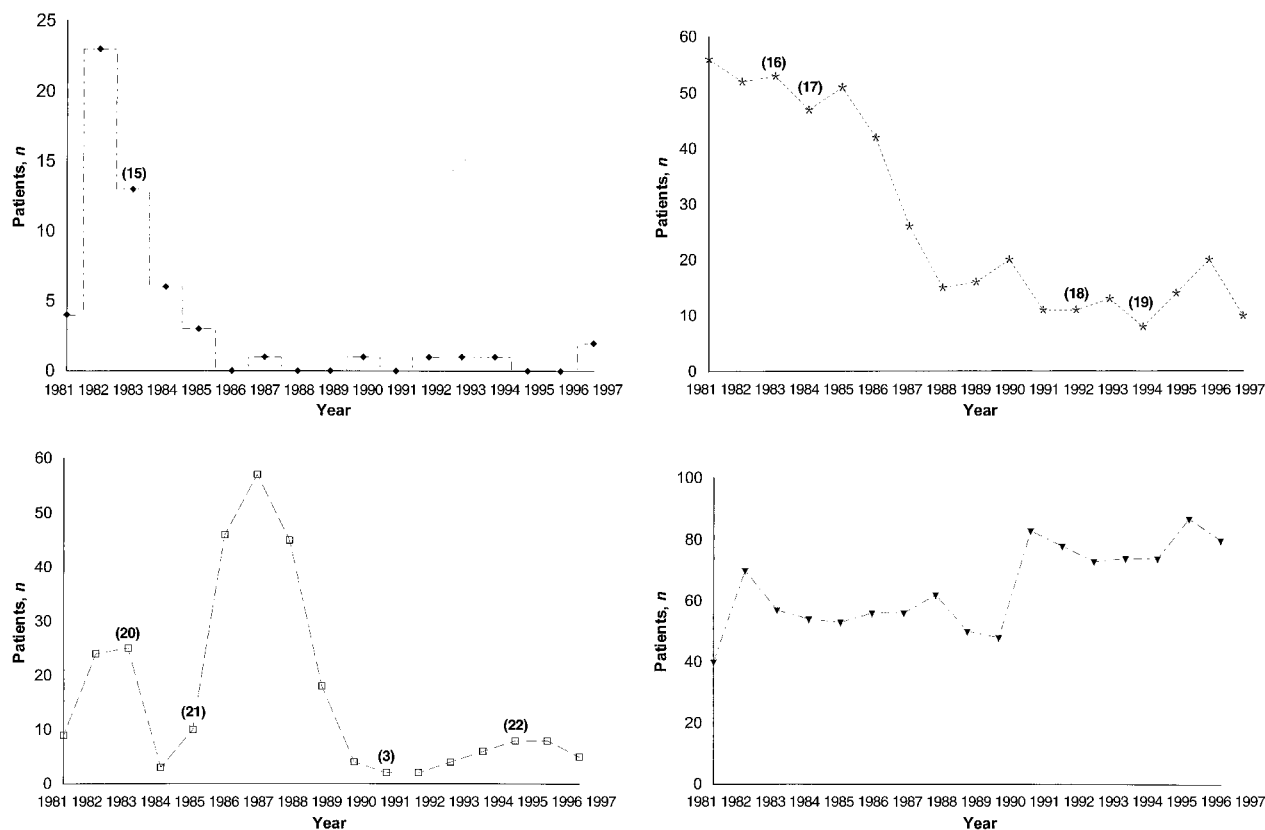


Figure 2. Changing trends in use of plasma exchange by members of the Canadian Apheresis Group (from 1981 to 1997) in patients with rheumatoid arthritis (top left), systemic lupus erythematosus (top right), multiple sclerosis (bottom left), and Waldenstrom microglobulinemia (bottom right). Numbers in parentheses are reference numbers.

Table 2. Evidence Supporting or Refuting Need for Plasma Exchange*

Study (Reference)	Diagnosis	Patients, <i>n</i>	Study Design	Control	Outcome
Rock et al. [Canadian Apheresis Study Group] (1)	Thrombotic thrombocytopenic purpura	102	Parallel, randomized, controlled, nonblinded	Plasma infusion	Decreased mortality rate; increased platelet response rate
Gajdos et al. [Myasthenia Gravis Clinical Study Group] (8)	Myasthenia gravis	87	Parallel, randomized, controlled, nonblinded	Intravenous immunoglobulin	No difference in myasthenic muscular score
Dyck et al. (9)	Chronic inflammatory demyelinating polyneuropathy	29	Parallel, randomized, controlled, double-blind	Sham plasma exchange	Improved combined nerve conduction
Hahn et al. (4)	Chronic inflammatory demyelinating polyneuropathy	18	Crossover, randomized, controlled, double-blind	Sham plasma exchange	Improved clinical and selected physiologic measures
Dyck et al. (10)	Chronic inflammatory demyelinating polyneuropathy	20	Crossover, randomized, controlled, single-blind	Immunoglobulin	Similar improvement in clinical and electrophysiologic measures
Guillain Barré Syndrome Study Group (11)	Guillain-Barré syndrome (acute cases)	245	Parallel, randomized, controlled, nonblinded	No plasma exchange	Improved outcomes and clinical grade
French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome (12)	Guillain-Barré syndrome (acute cases)	556	Parallel, randomized, controlled, nonblinded	0 compared with 2 plasma exchanges 2 compared with 4 plasma exchanges 4 compared with 6 plasma exchanges	Onset of motor recovery, time to walking with assistance, 1-year muscle strength recovery, and time on ventilation
van der Meché et al. [Dutch Guillain-Barré Study Group] (13)	Guillain-Barré syndrome (acute cases)	150	Parallel, randomized, controlled, nonblinded	Immunoglobulin	Similar improvement at 4 weeks by 1 grade of motor function
Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group (14)	Guillain-Barré syndrome (acute cases)	383	Parallel, randomized, controlled, single-blind	Immunoglobulin	Similar improvement in disability, group grade, and vital capacity
Wei et al. (16)	Systemic lupus erythematosus	20	Parallel, randomized, controlled, double-blind	Sham plasma exchange	Improved serologic outcome but no difference in clinical outcome
Clark et al. (17)	Systemic lupus erythematosus	39	Parallel, randomized, controlled, nonblinded	No plasma exchange	Trend for reduction in serum creatinine concentration
Lewis et al. [Lupus Nephritis Collaborative Study Group] (18)	Systemic lupus erythematosus	86	Parallel, randomized, controlled, nonblinded	No plasma exchange	Improved serologic outcome but no difference in clinical outcome
Hauser et al. (20)	Multiple sclerosis	58	Parallel, randomized, controlled, nonblinded	No plasma exchange plus ACTH or intravenous cyclophosphamide plus ACTH	Trend for stabilization or improvement in four quantitative scoring systems
Khatri et al. (21)	Multiple sclerosis	59	Parallel, randomized, controlled, double-blind	Sham plasma exchange	Improved by 1 step on the standardized Kurtzke Disability Status Scale
Canadian Cooperative Multiple Sclerosis Study Group (3)	Multiple sclerosis	168	Parallel, randomized, controlled, double-blind	Sham plasma exchange or no plasma exchange	No difference in the expanded disability status scale score between groups throughout the study

* ACTH = adrenocorticotropin hormone.

trial with immunoglobulin infusion that followed the study allowed the authors to establish the minimum dosage needed to maintain normal, or almost normal, function in patients with chronic inflammatory demyelinating polyneuropathy. The authors believed that the cost of immunoglobulin infusion and that of plasma exchange were approximately the same. Because the trial demonstrated no definitive difference in efficacy between these two treatments, the ease of immunoglobulin use may make this therapy preferable. After publication of the study by Dyck and colleagues (10), this preference was reflected in a small decrease in the use of plasma exchange until

the successful results of the CAG controlled study on plasma exchange by Hahn and coworkers (4) was published in 1996 (**Figure 1**). Plasma exchange and immunoglobulin seem to be viewed as induction agents that must be supported by long-term immunosuppressive therapy.

Waldenstrom Macroglobulinemia

Waldenstrom macroglobulinemia, a hematologic disorder, was the fourth most common indication for plasma exchange in 1997 and the fifth most

common in 1981 (**Table 1**). In 1959, a metabolic balance study of a patient with Waldenstrom macroglobulinemia was published (36). After a 15-day control period, 500 mL of blood was removed each day for 15 days. The plasma was separated *ex vivo*, and the red cells were reinfused. This is the first record of the use of plasma exchange in the treatment of hyperviscosity in patients with Waldenstrom macroglobulinemia; however, a more thorough report of two cases (37), published in 1960, underscored the importance of plasma exchange in such patients. In this detailed study, two patients with hyperviscosity secondary to Waldenstrom macroglobulinemia were treated with a repeated series of plasmapheresis (37). Their symptoms were closely correlated with macroglobulin levels, and the reduction of these levels by plasmapheresis was associated with alleviation of clinical symptoms. Many reports have included much larger numbers of patients than these two studies, but the initial report (36) and the more detailed follow-up study (37) document the benefit of plasma exchange for patients with hyperviscosity secondary to Waldenstrom macroglobulinemia. The gradual increase in the number of patients undergoing plasma exchange may also reflect the anecdotal observation of Buskard and coworkers (38). They reported on two patients with Waldenstrom macroglobulinemia who had become resistant to cytotoxic drugs and subsequently received successful long-term treatment with plasma exchange every 4 to 6 weeks (**Figure 2**).

Acute Cases of the Guillain-Barré Syndrome

The role of plasma exchange in acute cases of the Guillain-Barré syndrome was established in 1985. A large randomized, controlled study compared plasma exchange with conventional therapy in 245 patients with acute, recent-onset cases of the Guillain-Barré syndrome (11) (**Table 2**). At 4 weeks, the authors noticed statistically significant differences in the plasma exchange group in time to improvement of one clinical grade, time to independent walking, and outcome at 6 months. Plasma exchange activity had been present before the study; however, 1 year after study publication, the use of plasma exchange increased sharply until 1995 (**Figure 1**). The conclusions of this report were augmented in 1997 by the French Cooperative Group's nonblinded study of plasma exchange and acute cases of the Guillain-Barré syndrome (12), which tried to determine the appropriate number of plasma exchanges that should be used for treatment (**Table 2**). This study concluded that patients with mild symptoms should receive 2 plasma exchanges

and that patients with moderate or severe disease who are unable to walk or are ventilator dependent should receive 4 plasma exchanges.

We have noted a recent marked decrease in the use of plasma exchange for the treatment of acute cases of the Guillain-Barré syndrome; this probably reflects the results of two large studies (13, 14) (**Table 2, Figure 1**). The Dutch Guillain-Barré Study Group conducted a randomized, controlled study to compare the efficacy of intravenous gammaglobulin with that of plasma exchange in terms of a 1-grade improvement in strength and median time to improvement (13). The study was nonblinded. In an attempt to control bias during follow-up, one of the study coordinators, who was unaware of the treatment assignment, evaluated every patient once; the scores were compared with those assigned by the individual investigators. Thirty-four percent of patients treated with plasma exchange and 50% of patients treated with intravenous immunoglobulin showed strength improvement by 1 grade or more. In addition, the intravenous immunoglobulin group had fewer complications and less need for artificial ventilation; this finding suggests that intravenous immunoglobulin was as effective as or superior to plasma exchange in the treatment of acute cases of the Guillain-Barré syndrome. The results of this study did not immediately affect the use of plasma exchange, but by 1995, a sharp and continuing decrease in activity was seen (**Figure 1**).

The findings of the Guillain-Barré Study Group were confirmed by a study from the Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group (14) (**Table 2**). This was a single-blind, randomized study of plasma exchange, intravenous gammaglobulin, and plasma exchange plus gammaglobulin in patients with acute cases of the Guillain-Barré syndrome who had had onset of neuropathic symptoms in the previous 14 days and were now unable to walk independently. Intention-to-treat differences were not statistically significant. Efficacy with plasma exchange and intravenous immunoglobulin increased slightly but did not justify the greater inconvenience, costs, and risks of the combined regimen. Therefore, the decreasing number of plasma exchanges in patients with acute cases of the Guillain-Barré syndrome may reflect the change from a reliance on plasma exchange to an acknowledgment of equal or possibly superior efficacy for intravenous immunoglobulin (13, 14) (**Figure 1**).

Rheumatoid Arthritis

In 1982, 347 procedures (7.5% of all plasma exchanges) were performed in patients with rheumatoid arthritis, making it the fifth most common in-

dication for plasma exchange. This number rapidly decreased after publication of a 1983 double-blind crossover study by Dwosh and colleagues (15) of 26 patients with rheumatoid arthritis who were unresponsive to anti-inflammatory and slow-acting rheumatic drug therapy (**Figure 2**). All patients received 10 true and 10 sham plasma exchanges. Twenty patients completed the study, and 6 were withdrawn (3 because of poor venous access). A paired *t*-test analysis of seven clinical measures did not show a significant difference between the two procedures, although transient mild improvement occurred during both types of plasma exchange (possibly because of a placebo effect). In this study, the magnitude of improvement in patients who received a sham treatment was similar to that in patients who received placebo medication for rheumatoid arthritis in other therapeutic trials. The study by Dwosh and colleagues (15) demonstrated the potent placebo effect of plasma exchange and does not support the use of plasma exchange as primary adjunctive therapy in patients with chronic rheumatoid arthritis. This negative report by the CAG resulted in a prompt and permanent decrease in the use of plasma exchange for the treatment of rheumatoid arthritis (**Figure 2**).

Systemic Lupus Erythematosus

Systemic lupus erythematosus was the second most common indication for plasma exchange in 1981, but by 1997, less than 0.4% of the procedures were done in patients with this disorder (**Table 1, Figure 2**). Jones and coworkers (39) noted that 4 patients with high levels of circulating immune complexes experienced a striking clinical and immunochemical improvement, whereas 4 patients with only minor complement disturbances and no direct evidence of circulating immune complexes did not seem to benefit from plasma exchange (39). The first prospective controlled study (16), a randomized, double-blind, placebo-controlled study of 20 patients with mild systemic lupus erythematosus, was published in 1983 (**Table 2**). Both phases of the study showed improvement or no change at each of the evaluation points, which confirmed the original observation that plasma exchange was of little benefit to patients with relatively mild systemic lupus erythematosus.

The next randomized, controlled study, reported in 1984 (17) (**Table 2**), showed a reduction in serum creatinine concentration in the plasma exchange group and an increase in serum creatinine concentration in the non-plasma exchange group. This reduction was not statistically significant. The authors indicated that it was unclear whether similar modest

benefit might have been demonstrated by an increase in medication. Two years after publication of this study, plasma exchange to treat patients with severe systemic lupus erythematosus had gradually and progressively decreased (**Figure 2**).

By 1992, few plasma exchanges were being done in patients with severe systemic lupus erythematosus. A 1992 multicenter study (18) involved 86 patients with severe lupus nephritis (focal, diffuse, or membranous glomerulonephritis). Patients had plasma exchange 3 times per week for 4 weeks. Drug therapy was standardized, and mean follow-up was 136 weeks (**Table 2**). No benefit was seen for clinical outcomes, as measured by serum creatinine concentration or urinary protein excretion, and the authors concluded that they could not recommend plasma exchange as a treatment for severe lupus nephritis.

These conclusions led to a reexamination of the role of plasma exchange in patients with systemic lupus erythematosus. A multicenter international study by Euler and colleagues (19) attempted to determine whether cyclophosphamide plus plasma exchange was superior to cyclophosphamide pulses alone in the treatment of severe systemic lupus erythematosus. Patients were classified as having severe systemic lupus erythematosus by an inclusion scoring system that took into account manifestations in the central nervous system, leukocytoclastic vasculitis, nephritis, cardiopulmonary impairments, and hematologic impairments. The results of this study are yet to be published, but early reports suggest no statistically significant differences in outcome between the two groups. The slight increase in use of plasma exchange from 1995 and 1996 for systemic lupus erythematosus may have been associated with trial activity, but by 1997, the negative nature of the study and its completion signaled a further decrease in use (**Figure 2**). The generally negative nature of all of these studies led to a gradual and significant decrease in the number of patients with systemic lupus erythematosus who were treated with plasma exchange (**Figure 2**).

Multiple Sclerosis

In 1986 and 1987, multiple sclerosis was the fourth most common indication for plasma exchange; in 1988, it was the fifth most common, representing approximately 10% of procedures in these three years. It now accounts for less than 0.4% of procedures (**Table 1, Figure 2**). A 1983 study (20) called attention to the possible role of plasma exchange as a form of treatment for chronic progressive multiple sclerosis. This three-group, randomized, nonblinded, controlled study examined three treatment regimens in patients with chronic

progressive multiple sclerosis (**Table 2**). The chief weakness of this study was that outcome assessment was based on nonblinded observations. The authors could not indicate that plasma exchange had no benefit because an inadequate number of patients were enrolled in the plasma exchange group of the trial, and the study was terminated because of the success of the intravenous cyclophosphamide therapy. A small nonblinded, controlled, prospective study (21) indicated a superior outcome in 30 patients who received immunosuppression and plasma exchange weekly for 20 weeks compared with 29 patients who received immunosuppression alone (**Table 2**). Use of plasma exchange significantly increased the year after this report was published (**Figure 2**); however, this increase may also have been related to the study by the Canadian Cooperative Multiple Sclerosis Study Group (3). This large randomized, controlled study, which included a placebo group and used end points based on blinded observations, showed no benefit for plasma exchange or immunosuppression (**Table 2**). Of interest, the nonblinded neurologist, in contrast to the blinded neurologist, attributed a less favorable outcome to patients who were in the placebo group. This well-constructed study pointed out the necessity of having blinded observations of functional outcomes over time. Our best explanation for the increased use of plasma exchange for patients with multiple sclerosis from 1986 to 1989 is the enrollment of patients in the Canadian Cooperative Multiple Sclerosis Study Group study (3) (**Figure 2**). The subsequent negative results of this study were apparent to CAG members before the report was published in 1991; this knowledge explains the decrease in activity that persisted until 1997.

In 1995, a meta-analysis by Vamvakas and colleagues (22) examined six randomized, controlled studies that assessed the effects of plasma exchange in patients with chronic progressive multiple sclerosis. The authors concluded that plasma exchange may be beneficial in patients with chronic progressive multiple sclerosis who were likely to experience neurologic decline during the ensuing 12 to 24 months. However, the report indicated that the results of the meta-analysis were not significant when only the findings of experimental studies that had used blinded evaluating neurologists were compared; this point is particularly important because the large study done by the Canadian Cooperative Multiple Sclerosis Study Group (3) indicated the potential for observer bias. Vamvakas and colleagues (22) suggested that further studies were needed. However, their study clearly outlines the fact that plasma exchange had no apparent effect if the studies were corrected for multiple comparisons, blinded observations, or exclusion of patients who

did not conform to standard entry criteria. This meta-analysis seems to have had no effect on an increase in use of plasma exchange by CAG members for the treatment of multiple sclerosis.

Conclusions

In 1981, 3189 plasma exchanges were performed by members of the CAG, of which 55% were for five disorders (myasthenia gravis, systemic lupus erythematosus, thrombotic thrombocytopenic purpura, acute Guillain-Barré Syndrome, and Waldenström macroglobulinemia). In 1997, the five conditions that most frequently indicated plasma exchange made up 81.1% of all procedures. In 1981, only 50% of the procedures for the five conditions that most frequently indicated plasma exchange had a published scientific basis; in 1997, however, 100% of the five most frequent indications for plasma exchange had a sound published evidence base. The changes in the order of the five conditions that most frequently indicated plasma exchange reflect the preeminent role of plasma exchange in the treatment of thrombotic thrombocytopenic purpura, a previously fatal disorder. The number of patients receiving plasma exchange from members of the CAG increased in 1991, at the time of the publication of the CAG 7-year study (1). The results, which were available to CAG members the previous year, seem to have had an immediate effect on a continuing increase in the rate of use of this procedure (**Figure 1**).

A similar significant increase was noted after 1985 in patients with acute cases of the Guillain-Barré syndrome, when a study that demonstrated the benefit of plasma exchange therapy (11) was published. It is interesting to note that the well-constructed 1992 study by the Dutch Guillain-Barré Study Group (13) did not have an immediate effect; this may reflect a slight ethnocentric bias. By 1995, the number of plasma exchange procedures done in patients with acute cases of the Guillain-Barré syndrome decreased sharply (**Figure 1**). We believe that this decrease is a result of increased use of intravenous immunoglobulin. A similar shift is noted in the data for chronic inflammatory demyelinating polyneuropathy, which began to show a decrease in 1994 and probably reflects the results of the controlled study by Dyck and colleagues (10). This study suggested that intravenous immunoglobulin and plasma exchange were of equal efficacy (10). The positive results of the CAG study of plasma exchange in 1996 may have contributed to the slight increase in the use of this procedure that was seen in 1996 and 1997 (4) (**Figure 1**).

The Canadian Rheumatoid Arthritis and Multi-

ple Sclerosis studies demonstrate a large number of procedures that were performed before the availability of published evidence (3, 15). By the time of publication, the number of procedures for rheumatoid arthritis and multiple sclerosis had decreased dramatically and continued to decrease further with the negative study results (**Figure 2**). The studies of systemic lupus erythematosus seem to have had less effect on the pattern of use of plasma exchange; however, the initial negative study by Wei and co-workers (16) and the faint benefit reported by Clark (17) in 1984 resulted in a gradual decrease in the application of plasma exchange (which was at an extremely low level before publication of the negative study by Lewis and colleagues in 1992 [18]). Use of plasma exchange in patients with systemic lupus erythematosus has not seen a new increase, coincident with the early negative results from the study by Euler and colleagues (19) (**Figure 2**). Before 1981, plasma exchange was proven to benefit patients with Waldenstrom macroglobulinemia and those with myasthenia gravis; use of plasma exchange for these two disorders has increased gradually and progressively (approximately 100%) over the 17 years of study. This trend is similar to the doubling in the number of overall procedures that was seen from 1981 to 1997 (**Figures 1 and 2**).

We suggest that in most cases, the pattern of change in the application of plasma exchange by members of the CAG reflects the availability of evidence largely obtained from controlled prospective studies. Although other centers, such as those in France, have similar centrally directed registries, we believe that the center-by-center review of use is unique to the CAG. The center-by-center review challenges medical directors to explain their current plasma exchange practices; it may also be partially responsible for the immediate effect of information on use even before publication of study results, such as that seen in patients with thrombotic thrombocytopenic purpura (1).

Appendix: Canadian Apheresis Group Regional Medical Representatives

Vancouver: N. Buskard and B. Benny; Edmonton: T. Kovithavongs and J. Janowska; Calgary: J. Klassen; Saskatoon: D. Sheridan; Regina: A. Devaraj; Winnipeg: D. Lane; Sault Ste. Marie: D. Walde; Sudbury: S. Gluck; London: W.F. Clark; Hamilton: R. Foley and M. Sternbach; Toronto: K. Shumak, D. Sutton, and J. Freedman; Kingston: P. Ford; Ottawa: G. Rock; Montreal: S. Caplan, C. Girouard, M. Champagne, J. Moquin, and L. Legault; Sherbrooke: L. Delisle; Quebec: P. LeBlond; Saint John: S. Dolan; Halifax: D. Anderson; St. John's: B. Barrett.

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