Appendix B.—Apheresis for Hemolytic-Uremic Syndrome

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The most prominent feature of hemolytic-uremic syndrome (HUS) is renal microangiopathy, which is characterized by endothelial damage in glomerular capillaries and renal arterioles. The event which initiates this endothelial damage is unknown although some authors have suggested that endotoxin is a prime candidate (71). The damaged endothelial cells become swollen, leading to renal ischemia and decay of kidney function and two secondary hematologic events—red cell destruction (hemolytic anemia) and a dramatically reduced level of circulating platelets (thrombocytopenia). The former results from mechanical damage to red cells passing through the damaged vessels. The reduced platelet count results not only from trauma but also localized intravascular coagulation (and platelet consumption) occurring in the damaged vessels.

An alternative and more recent hypothesis cites decreased formation of PGI_2, (prostacyclin) as the precipitating event leading to the full-blown clinical manifestation of the syndrome (instead of a toxic agent such as endotoxin). The finding of $PG1_2$ deficiency in adults and children with HUS supports this concept (11). In this case, the loss of PGI_2, causes localized platelet aggregation in renal vessels and vascular obstruction. Traumatic red cell destruction (hemolytic anemia) is a corollary of the development of the microthrombi which partly occlude the vascular lumens (84).

Finally, Seger, et al. (126), have suggested that HUS is a polyetiologic syndrome with neuraminidase being the culprit agent in some cases, particularly among children suspected of having pneumococcal infections, as this agent can produce lesions in all three cell systems (red blood cells, platelets, and endothelial cells).

The hemolytic-uremic syndrome shares a number of features, including vascular endothelial damage, with thrombotic thrombocytopenic purpura (TTP). In fact, HUS has been considered by some clinicians to be a variant of TTP, this being supported by similar overlapping clinical and pathologic characteristics and the possibility of similar precipitating events. There is no objective method at present to distinguish HUS from TTP, although in the case of the former, the kidney is typically the main and often **only target organ, children are primarily affected, and the prognosis is generally much better (71). These authors believe, however, that a clinical diagnosis of one or the other conditions must be made because the treatment differs and in HUS, depends on the management of the complications associated with renal failure.**

Plasma exchange (PE) was first administered as a therapy for TTP in 1959 by Rubenstein and others (84). Rapid and sustained recovery was observed after two exchange transfusions with fresh whole blood to an n-year-old patient.

Taft and Baldwin (132) noted that centers which have experience with five or more patients diagnosed with TTP and treated with PE are reporting survival rates in the 60- to 80-percent range. Plasma exchange is now being advocated as a potential therapy for treating HUS because of the suspected etiological similarity between the syndrome and TTP. Apheresis is viewed as being potentially helpful in removing a toxic agent (e.g., endotoxin, neuraminidase) or replacing a missing factor, possibly a physiological inhibitor of platelet aggregation. In the latter case, Beattie, et al. (11), and Misiani, et al. (84), have both suggested that PE using normal plasma replaces a missing factor needed for stimulating PGI_2 production by vascular endothelium.

Specification of Treatment

Only eight reports (including two letters to the editor and one abstract) have been published in the English medical literature on the effectiveness of plasma exchange in the management of HUS. These eight communications account for 11 patients diagnosed with HUS ranging in ages from 1½ to 59 years who were treated as an ancillary therapy with corticosteroids, antiplatelet drugs, or heparin. * Moreover, in seven

● Beattie, et al. (11), report on a 3%-year-old boy diagnosed with HUS. The patient was initially treated with aspinn and dipyrimadale (s mg/kg/day) and his condition gradually improved. Plasma exchange was not initiated until 10 days later when the patient was readmitted to the hospital with recurrent symptoms of HUS. The authors do not indicate whether any drug therapy was administered during the second episode, so it is assumed that PE was the only therapy administered. The article by Taft and Baldwin (132) focuses primarily on the treatment of patients diagnosed with TTP. They only briefly mentioned two patients with HUS who were treated with apheresis and do not provide full case histories.

cases hemodialysis or peritoneal dialysis was performed concurrently with plasma exchange.

It appears that apheresis is not the sole treatment regimen of HUS and thus the particular impact on patient health may be hard to determine. Apheresis is commonly embedded within a more comprehensive treatment regimen including a variety of drugs, some form of dialysis, and blood or platelet transfusions. Several authors (84,132) have mentioned the difficulty in evaluating the efficacy of each treatment approach alone since different forms of therapy have typically been employed in combination. Misiani, et al. (84), for example, are concerned with separating the beneficial effects of PE from antihypertensive drugs in treating HUS, whereas Taft and Baldwin (132) emphasize the need to evaluate the relative contributions of ancillary therapies such as corticosteroids and antiplatelet drugs to the successful recovery of PE-treated patients.

Despite the fact that a sizable proportion of HUS patients are treated with some form of dialysis, none of the authors point out the possible confounding effects of hemodialysis and peritoneal dialysis performed concurrently with plasma exchange. It should be noted that dialysis may provide beneficial effects independent of apheresis. In the case of hemodialysis, all patients are heparinized during dialysis. Heparin, an anticoagulant drug, exerts an antithrombotic effect. Recall that thrombotic occlusions of capillaries and arterioles have been implicated in the pathogenesis of HUS. Thus, hemodialysis (which necessarily includes the administration of heparin) may be partly responsible for inhibiting the formation of microthrombi in the glomerular capillaries and thereby increasing renal blood flow.

Heparin was also administered to one HUS patient in the absence of hemodialysis, which suggests that clinicians recognize the potential efficacy of using heparin therapy alone for treating HUS. Parnes, et al. (106), report on two small series of HUS patients treated with only heparin; mortality rates of 9 and 50 percent were recorded. In each series, about 30 percent of the patients completely recovered; the remaining underwent chronic dialysis.

In the case of either hemodialysis or peritoneal dialysis, it may also be postulated that the removal of unspecified substances of low molecular weight may ameliorate the symptoms of HUS, if the substances that are removed are responsible for the development of the vascular lesions.

It is important to draw a distinction between plasma exchange and plasma infusion. In the former case, plasma is removed and replaced by a colloid solution, commonly albumin, fresh frozen plasma, or simple donor plasma. Although the plasma replacement in early cases was initiated only for purposes of expansion of the intravascular volume, later authors suggested that the administration of fresh frozen plasma had an independent therapeutic effect. This led some investigators to administer it alone with apheresis; this is described in the literature as plasma infusion. The beneficial effects of PE may be confounded when plasma infusion is also administered as part of the treatment regimen. Obviously, both methods have the advantage of replacing the missing plasma factor, if, in fact, that is the underlying cause of HUS. However, PE may provide the additional advantage of removing other possible etiological agents, the products of damaged red blood cells, and other hypothetical platelet aggregating substances. In short, when these two forms of therapies are both administered during a relatively short period of time as in the case of two HUS patients described in the literature (84) it becomes difficult, if not impossible, to attribute any measure of success to one therapy or the other.

It is conceivable that some form of adjuvant drug therapy or dialysis is required in conjunction with apheresis to successfully treat patients with HUS. That is to say, clinicians may view PE as a necessary but not sufficient form of treatment to restore normal physiological functions. When other forms of therapy are used in addition to PE, particularly drug therapy, there still is the problem of operationalizing the treatment when the concomitant therapies vary widely across cases (e.g., the use of heparin with or without platelet inhibitors). When there is differential improvement by type of drug used, the integrity of the treatment is called into question. It may be the case that the synergistic effects of apheresis and drug therapy may vary according to the dosage and regimen of the particular drug used.

Plasma exchange therapy itself varies widely with respect to the number of exchanges performed and the volume of plasma removed at each exchange process. Table B-1 shows that the number of PEs performed for each episode of HUS ranges from one to eight exchanges for the 11 patients diagnosed with HUS. In two of the studies, the frequency of plasma exchange appears to be dictated by the platelet response (spontaneous increment v. lack of increment), and the level of serum LDH activity or creatinine levels. In one study, however, the frequency of plasma exchange in another study depended on the resolution of neurologic symptoms *(sO).* As best as can be determined from table B-1, the volume of plasma removed at each exchange is variable. However, the discrepancy in the volume of plasma removed at each exchange across patients may be due to the fact that 7 of the 11 pa-

Table B-1.—Apheresis Experience Among Patients Diagnosed With Hemolytic-Uremic Syndrome

Study reference number	Number of patients	Age range of patients	Range of plasma exchanges performed per episode	Range of plasma volume removed per exchange	Types of replacement fluids used
	1	3½ yrs.	2	1,000 ml	Fresh frozen plasma
1	2	7 yrs.	3	Unknown	Whole blood
5	2	54-56 yrs.	1	3,000 ml	Fresh frozen plasma
6	1	21 yrs.	5	3,000 ml	Fresh frozen plasma and normal saline
7	2	19-22 mo.		1,500 ml-2,350 ml	Whole blood
8	1	8 yrs.	8	1,500 ml	Albumin, fresh frozen plasma
9	2	2-7 yrs.	1-6	27 ml/kg-89 ml/kg	Whole blood, fresh frozen plasma
10	1	37 yrs.	4	Unknown	Unknown

SOURCE: Office of Technology Assessment, 1983.

tients undergoing PE were children, who have smaller blood volumes. Table B-1 also shows that whole blood and fresh frozen plasma are the two most common replacement fluids used in the process of plasma exchange for patients with HUS. Human serum albumin was used as a replacement fluid in only one case and the authors noted that there was no improvement after three exchanges, suggesting that no circulating agent perpetuated the condition. Plasma exchange was then performed with fresh frozen plasma, which was followed by a prompt recovery in the platelet count (131).

The absence of explicit and detailed protocols for performing plasma exchange poses a major problem in the evaluation of the effectiveness of apheresis therapy. However, given the rare occurrence of HUS in the population, it comes as no surprise that not enough information has been accumulated on the use of plasma exchange to develop such protocols.

Misiani, et al. (84), suggest that at the present time it is impossible to define individual PE requirements since both the patient's and donor's plasma may differ with respect to the plasma factor (e.g., PGI_2) concentrations. Those authors recommend apheresing a full volume at the initial exchange, followed by one-half the initial amount daily until full hematologic remission is obtained. The literature on TTP, on the other hand, is considerably more extensive and consequently, a set of treatment guidelines or protocols has recently been proposed by Taft and Baldwin (132). They have developed a clinical scoring system (including necrologic evaluation) to evaluate the day-to-day severity of the disease, which maybe used to determine the frequency of PE. Relying on five clinical criteria (i.e., platelet count, serum LDH, total bilirubin, creatinine, and necrologic status) a score is calculated to determine whether therapy should be continued. Since several investigators have suggested that HUS is a variant of TTP, it is conceivable that such a scoring system modified slightly to take account of the clinical manifestations specific to HUS could be used to determine the appropriate frequency and volume of PE.

Outcome Measures

A recurring critical issue in any attempt to analyze the effectiveness of a medical innovation is the selecting of appropriate endpoints for evaluating the success or failure of the innovation. In many instances, outcome measures are either lacking, not specified, or ill-defined in the written reports. For example, one study of HUS reports that the patient "showed improvement" after the PE was initiated, without defining precisely what improvement means (135).

It appears that on, the whole, nonspecification of outcome measures is less of a problem when evaluating the effectiveness of plasma exchange for patients with HUS. While it is noteworthy that none of the eight studies provide a discussion that specifically focuses on the kinds of outcome measures that should be used to evaluate apheresis for HUS, there does appear to be some consensus in the literature on the array of clinical indicators that are reported pre- and post-PE.

Table B-2 shows, for example, that all eight studies reported whether or not their patients underwent chronic dialysis and their mortality experience. However, the length of followup during which mortality data were collected varies across studies, which may limit the usefulness of directly comparing mortality rates, Furthermore, seven of the eight studies reported creatinine or BUN levels (i.e., indicators of renal insufficiency) and six studies indicated platelet counts. All six indicators displayed in table B-2 should be *con*sidered to be objective outcome measures. That is to say, none of these measures is likely to be influenced

Table B-2.—Variability in Effectiveness of Plasma Exchange Therapy for Hemolytic-Uremic Syndrome as Expressed in Selected Outcome Measures (all outcome measures relate to past plasma exchange period)

Study reference number	Number of patients	Outcome measures: Patients with increment in platelet count	Patients with eventual decline in serum LDH	Patients with remission of neurologic signs	Patients with eventual decline serum creatinine or BUN (renal improvement)	Patients for whom chronic dialysis was initiated or continued	Mortality
1	1	1/1	NA	NA	**0/1**	1/1	**0/1**
2	1	NA	NA	1/1	**1/1**	**0/1**	**0/1**
5	2	2/2	2/2	NA	**1/2**	**1/2**	**1/2**
6	1	1/1	NA	NA	**1/1**	**0/1**	**0/1**
7	2	NA	NA	NA	0/2	2/2	2/2
8	1	1/1	NA	NA	1/1	0/1	**0/1**
9	2	212	2/2	NA	212	0/2	0/2
10	1	1/1	NA	NA	1/1	0/1	0/0

NA-Not available.

SOURCE: Office of Technology Assessment, 1983.

by expectations of the physician or patient concerning the efficacy of treating HUS with apheresis.

These measures clearly represent endpoints that are evaluated at different times during a given episode of HUS. It may, in fact, be convenient to make a distinction between the more general measures of health status relating to HUS (e.g., chronic dialysis, mortality), which represent the sum total of many influences and the more sensitive and specific hematologic, biochemical, and clinical signs and symptoms (e.g., platelet count, creatinine, BUN, serum LDH levels, and neurological status) that often occur rapidly following plasma **exchange. The former may be called 'long-term" outcomes, whereas the latter may be termed "immediate" outcomes.**

When an outcome measure such as mortality is used to evaluate the effectiveness of apheresis therapy for HUS, the benefits of apheresis may be substantially understated. Plasma exchange may, for instance, bring about a temporary improvement in the patient's clinical status, but other intervening factors may ultimately cause the patient's death. Most clinicians, however, would probably agree that the ultimate objective of apheresis therapy is to increase the likelihood of survival, which suggests that survival (or mortality) is an important outcome measure of the efficacy of apheresis and should not be disregarded.

The need for chronic dialysis, on the other hand, may be a more appropriate outcome measure for determining the ultimate success of plasma exchange in the treatment of HUS, since renal failure is a major element of the syndrome. Chronic dialysis was deemed necessary for 4 of the 11 patients listed in table B-2 (two of whom later died) which represents a 36-percent failure rate when dialysis is used as the sole measure of the effectiveness of PE therapy.

Finally, changes in hematologic and biochemical parameters such as platelet count, serum LDH, creatinine, and BUN levels may also be used to evaluate the effectiveness of apheresis therapy. The difficulty with using these measures, however, is that patients may show improvement in one or all of those parameters yet still require long-term dialysis (e.g., patients in studies 1 and 5). In short, the "immediate" outcome measures may be necessary but insufficient indicators of the efficacy of plasma exchange. Perhaps these measures and the end points of chronic dialysis and mortality could be combined in some way as co-measures. The problem of combining multiple evaluation criteria and assessing the significance of the results is a difficult one. For example, researchers may choose to assign different weights to each outcome measure which would lead to disagreement and perhaps a lack of consensus on the effectiveness of PE in treating HUS.

Patient Selection

In seven of the eight studies, PE therapy was initiated when patients diagnosed with HUS did not respond to either hemodialysis or peritoneal dialysis or other conventional therapies including corticosteroids, antiplatelet drugs, or heparin. In other words, apheresis was performed on these patients as a last resort therapy when there were no other effective alternative therapies and death was the likely outcome. Since only the "worst cases" of HUS appear to be selected for apheresis therapy, it is possible that the effectiveness of plasma therapy is underestimated, depending on which outcome measure is used. If PE is initiated in the later stages of the disease (i.e., when end-stage renal disease is inevitable), the beneficial effects of

apheresis maybe dramatically reduced if chronic dialysis is the end point used for evaluating the effectiveness of the treatment.

Evaluation of the Evidence

The eight communications that have appeared in the literature during the past 3 years describing the effectiveness of apheresis in treating patients with HUS present data on a total of 11 patients, but each case is described individually. Only one of the communications suggests that PE has limited effectiveness on the disease process (11). However, the authors in this article add that the clinical benefit may have been compromised because PE was performed during a recurrent phase of the illness which is recognized as being associated with poor prognosis. The remaining seven studies are almost uniformly favorable in suggesting that apheresis contributes to clinical improvement, although there is no explanation provided about which measures are used to gauge this improvement. Several authors add the caveat that PE be initiated during the early stages of the disease in order to realize its full benefit (132). Parries, et al. (106), caution that PE alone is associated with complications (e.g., hepatitis) and that these risks should be weighed against the potential benefits of apheresis.

What can be said about the "scientific soundness" of the data on which the conclusion that PE is efficacious is based? Scientific soundness is defined here as the adequacy and the credibility of the available information for reaching a consensus. First, in the case of evaluating the use of PE therapy for treating HUS, it is quite clear that the newness of this particular application of the technique is associated with a small and incomplete research base. With only 11 patients, there is insufficient data on which to make a recommendation to endorse this procedure. Second, the credibility of the evidence is open to question because of the quality of research used in all eight studies; these case studies do not include any comparison groups. The major problem with the case-study approach (and other pretrial studies) is that they are subject to a variety of competing alternative explanations for the observed effects of the therapy. Interpreting the evidence becomes even more problematic when the potential affects of apheresis therapy are confounded by other therapies that are used concomitantly with plasma exchange. Apheresis was the single therapy used in only two case studies; one patient completely recovered and the other patient underwent chronic dialysis because of continued deterioration of renal function (11,106).

Finally, it is unclear as to which criteria (e.g., outcome measures) should be used in evaluating the effectiveness of the therapy. There are too few cases to determine whether there is high concordance between the "immediate" outcomes (e.g., platelet counts, LDH, creatinine, and BUN levels) and the "long-term" outcomes (e.g., chronic dialysis, mortality). If these measures turn out to be discordant, some method will have to be developed to combine these multiple evaluative criteria in order to arrive at the recommendation.