Appendix C.—Apheresis for Inhibitors to Factor VIII

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Factor VIII Antibodies

Apheresis, and more specifically, plasma exchange (PE), has been investigated as a potential therapy for patients with antibodies or inhibitors to Factor VIII during the past 10 years. Factor VIII is essential to achieve hemostasis (i.e., permit normal blood clotting and end bleeding). For that reason, patients with classic hemophilia have been particularly at risk from complications associated with the development of Factor VIII antibodies. It has been estimated that as many as 20 percent of such patients may develop this condition. Factor VIII inhibitors can also arise spontaneously in other patients. This so-called idiopathic or acquired inhibitor to Factor VIII can occur in women in their first year after childbirth, persons with rheumatoid arthritis, the elderly, and persons suffering a variety of other disorders.

The major concern in these situations has been to return Factor VIII to normal or effective levels. Treatment typically involved immediate and continued doses of human Factor VIII concentrate. This treatment often failed since it did not remove existing antibodies in the blood and frequently appeared to stimulate the production of more antibodies. To deal with these complications a variety of alternative treatments has been investigated. One of these has involved the use of apheresis with or without Factor VIII. The following sections summarize the available scientific research reporting on the use of PE in treating patients with antibodies to Factor VIII.

Literature Reviews

Twenty articles were located and retrieved from a MEDLARS search of the research literature. Four of these articles did not deal specifically with cases involving Factor VIII, five were in a foreign language (two in Russian, two in German, and one in Hungarian), one article was a duplicate copy of another, and one contained the same case information as another by the same authors. Of the foreign language articles, the two in Russian were excluded, the one in Hungarian also was published in English and that article was included in our review; the two German studies were read. One of the German articles did not deal with Factor VIII and the other presented a very brief case drawn from 210 patients and also was not included in this review.

There remained nine articles to review after the various exclusions were made. The articles were all case studies involving from one to six patients. Five studies reported treating a single patient; two had two patients; one had three, and another had six. Of the 18 patients in these nine studies, 10 had classic hemophilia, seven idiopathic Factor VIII antibodies, and one had von Willebrand's disease. The patients generally faced a life-threatening situation. Thirteen had severe bleeding and three required or were recovering from surgery. The patients ranged in age from 3 to 77 and generally had either low levels of Factor VIII or high levels of Factor VIII inhibitor reported prior to treatment.

Table C-1.—Apheresis Experience Among Patients Diagnosed With Inhibitor to Factor VIII

Study reference number	Number of patients	Range of PEs per episode	Range of plasma volume removed per exchange (in ml)	Replacement fluids used	Duration (days)
1	1	9	500-1,500	FFP[a], saline	42
2	1	2	3,800-7,500	FFP	21
3	2	6-8	1,500-3,000	FFP, albumin	8-10
4	3	1-2	1,500-3,000	Gelatin, albumin, saline	2-50
5	1	3	17,100 total	FFP	1
6	1	3	1,400-6,000	FFP	7
7	1	3	600-1,000	FFP	18
8	2	3-15	4,000	FFP, saline	3-14
9	6	1-4	2,500-3,500	Gelatin, plasma protein	1-4

[a]FFP = Fresh, frozen plasma.

SOURCE: Office of Technology Assessment, 1983.

Specification of Treatment

Although apheresis was employed in all of these studies, the actual definition or specification of treatment varies widely from one report to another (see table C-1). First, the number of PEs vanes widely from just 1 (109,143) to 15 (129). The modal number of PEs was three (occurring in six of the *18* patients) with another four receiving two exchanges. The volume of plasma actually exchanged also differed widely from one study to the next, ranging from 500 to 6,000 ml per exchange. The replacement fluid also varied. Although in seven studies fresh frozen plasma was used, other fluids included albumin, gelatin, plasma protein, and saline (or plasma expander). It should be noted that in most patients who were severely compromised fresh frozen plasma was used. The treatment also varied in duration, lasting from 1 day to *6* weeks.

Perhaps most troublesome in determining the appropriate treatment regimen is the use of immunosuppressants such as azathioprine and cyclophosphamide in conjunction with apheresis. Five of the eight studies used one of them simultaneously with PE and two had tried it before using PE. Nevertheless, there is a great difference of opinion on the value of such therapy despite its confounding with apheresis. One study (129) claims that "immunosuppression has not been shown to be effective and may well interfere with wound healing and increase susceptibility to infection." However, another study (111) concludes that "a combination of specific immune suppression and intensive . . . (apheresis) . . . may be the best form of treatment in patients with acquired idiopathic factor VIII inhibitors and life-threatening bleeding." The resolution of these conflicting claims and the separation of the two treatments (PE and immunosuppression) poses some difficulties in so few studies.

The study by Pintado, et al. (111), contains the best discussion of possible alternative treatments. In that study one elderly patient with idiopathic or acquired Factor VIII inhibitor was given six plasma exchanges over a 2-week period. These researchers reviewed the previous literature and concluded that "spontaneous remission of the immune response" (i.e., termination of production of Factor VIII antibodies) was "unlikely." Instead, they feel that the remission was due to the combined use of immunosuppressants and "antigenic load" (i.e., human Factor VIII concentrate).

Treatment with Factor VIII concentrate poses an additional problem in determining the efficacy of apheresis. As noted in the introduction, Factor VIII supplementation is viewed as the primary treatment with apheresis an adjunct to improve its efficiency. The use of Factor VIII was, in fact, reported in all nine studies encompassing 16 of the 18 patients treated. However, in one study (37) involving two patients, this treatment was evidently discontinued just prior to apheresis because of a rise in inhibitor level in one patient and an adverse reaction (to a porcine derivative) in the other. Similarly, in the study by Piller, et al. (109), one of three patients was treated with Factor VIII concentrate just prior to apheresis. While the inhibitor level was reduced from 1.3 to 0.5, p/ml, the goal of this study was its complete neutralization and an increase in Factor VIII. In the remaining two patients (who were not in a life-threatening situation) apheresis using Factor VIII-free solutions was tried in an attempt to prevent the "rapid increase" in inhibitor activity. In both cases there was a "less rapid" return of inhibitor activity to its previous level (and, in one case, a "considerably higher" level). The authors conclude that inhibitor levels can be lowered through "repeated . . . (apheresis) . . . at intervals of about one month."

The Piller, et al. (109), study did not employ immunosuppressants concurrently in conjunction with apheresis (although one patient received prior treatment with azathioprine and Factor VIII with cyclophosphamide "without success"). If the hypothesis of Pintado, et al. (111), is correct, then antibodies would continue to be produced requiring regular PE. As noted

Table C-2.—Effectiveness of Apheresis for Factor VIII Inhibitors

	Immediate		Followup
Study reference number	Hemostasis	Factor VIII inhibitor *(μ/ml)*	Factor VIII inhibitor *(μ/ml)*
1	—	1.2	0.8
2	yes	36	8
3	yes	1-8	0-1
4	—	O-4.8	0-17
5	yes	—	0
6	yes	—	0
7	yes	12	0
8	yes	—	
9	yes	0-1	5-47

SOURCE: Office of Technology Assessment, 1983.

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this is exactly the conclusion of Piller, et al. (109). Moreover, the two studies with the greatest number of PEs did not use immunosuppressants. In the study by Slocombe, et al. (129), noted above, one of the two patients received 15 PEs exchanges along with varying doses of Factor VIII. Similarly, Cobcroft, et al. (23), performed nine apheresis treatments on a patient (who had previously had unsuccessful immunotherapy). One can only speculate on whether as many exchanges would have been required had immunosuppressants been employed concurrently. In both studies, however, there is little justification provided for additional exchanges beyond the first two.

In summary, the modal regimen in the research studies involved two or three apheresis treatments in conjunction with both immunosuppressants (typically cyclophosphamide) and Factor VIII concentrate (from humans). Two hypotheses seem tenable from these studies. First, immunosuppressants may stop the production of antibodies as Pintado, et al. (111), claim, with the apheresis quickly removing existing antibodies. And second, apheresis using Factor VIII-free solutions such as gelatin or saline may slow the return of the inhibitor activity as Piller, et al. (109), maintain. The two treatment therapies are clearly not independent and could be combined. At present there is a need for more systematic research on the most appropriate treatment for patients presenting with Factor VIII antibodies.

Results of Treatment

The results of the treatment just described in the nine studies reviewed are presented in table C-2. Both short-term or immediate results and long-term findings are indicated. For 16 of the 18 patients at risk due to severe bleeding or surgery the immediate clinical results were uniformly successful. In all cases hemostasis was achieved and the patient fully recovered from the acute episode. One should note, of course, that cases of clinical failures are much less likely to be submitted or accepted for publication.

The measures of Factor VIII inhibitor (in ~/ml) and Factor VIII (in percent normal) are not consistently reported in the text. Where possible this information was recorded or interpolated from tables and figures. These figures indicate a less than consistent pattern of results. In almost half the patients (i.e., 8 of 18) the inhibitor level falls below 2 @ml at followup; while in 9 of the patients reported, the inhibitor level is 8 µ/ml or greater. The inhibitor data for one patient (129) were not available, but were probably very low given the Factor VIII level of 75 percent.

Eight of the nine patients with poor long-term results are from just two studies (109,143). The Piller, et al., study differed from all the others in that its sole objective, as noted earlier, was the long-term reduction in the Factor VIII inhibitor level. This study did not employ Factor VIII therapy along with immunosuppressants in the two failed cases (although one had received them earlier). It should be noted that short-term control was achieved and the authors conclude that one could "treat severe hemorrhages immediately by only administering Factor VIII or by combining one . . . (apheresis) . . . run with replacement therapy."

The other six patients, one-third of the total from all of the studies, with poor long-term or "secondary rise" in the inhibitor level, were treated by Wensley, et al. (143). In this case, apheresis combined with human Factor VIII concentrate produced an initial lowering of the inhibitor level to permit hemostasis and healing. The authors recommend this combined therapy as a better alternative to using "significant quantities" of Factor VIII alone.

As noted in the previous section, the impact of immunosuppressants should be considered. Neither of these two studies reported the concurrent administration of immunosuppressants to patients. On the other hand, five of the six patients treated with immunosuppressants had followup inhibitor levels of 1 @ml or less.

Evaluation of the Evidence

In conclusion, it is important to ask what one can infer from these nine studies. To do this, it is useful to consider the quality of the research evidence provided. A number of points should be considered in reaching an overall assessment.

First, the studies are all pretrial clinical reports generally of one patient (i.e., the five articles). There were no clinical trials comparing a number of patients systematically treated by a number of well-defined therapies. In fact, other than references to some prior treatment regimen there is no comparative information available.

Second, as an earlier section noted, there is no agreed upon treatment for patients with inhibitors to Factor VIII. While apheresis is used and endorsed in all nine studies, the treatment is more complex than that. Other concurrent therapies are described with varying results and the number of PEs also differed from study to study. While a number of possible hypotheses were examined, the evidence is far from con-

elusive on what is the best method to treat this condition.

Third, the goals of the studies also differed. Most involved acute, life-threatening situations, usually episodes of severe bleeding. In those cases, short-term resolution of the problem was sought and generally achieved. In a few other studies, longer term solutions to the anti-Factor VIII were attempted with varying results. Here too, there are possible treatment combinations that need to be further investigated.

Finally, with so few patients in so few studies one must consider the issue of sample bias. It would only take a few reports of a few patients with differing or negative results to alter one's notion of the efficacy of apheresis in this situation. For this reason the evidence can only be viewed as preliminary and provocative. It is far from persuasive.

Apheresis in combination with other therapy is only an emerging technology for treating patients with Factor VIII antibodies. There is a need for more careful study and specification of the treatment and its effects—both of immediate and longer duration. There are a number of questions that need to be answered before its efficacy is established. If, as is likely, apheresis continues to be employed in life-threatening situations, then physicians should be encouraged to undertake more systematic study of the treatment. This could include a number of therapeutic alternatives systematically applied to a series of patients, perhaps in a controlled trial.

In conclusion, it should be noted that some experts believe all the treatment combinations described above are not effective. In particular, PE is viewed as a stopgap measure, at best, because (as the literature indicates) the antibody titer rapidly increases post exchange. For these reasons current interest has focused on bypassing the blockade of the Factor VIII inhibitor by administering new agents that contain a mixture of clotting factors, including activated Factor VIII. Given the availability of these new agents, such treatment may be the therapy of choice for patients with high titers of Factor VIII antibodies.