IMPROVED SURVIVAL IN THROMBOTIC THROMBOCYTOPENIC PURPURA–HEMOLYTIC UREMIC SYNDROME

Clinical Experience in 108 Patients

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Abstract *Background and Methods.* Thrombotic thrombocytopenic purpura–hemolytic uremic syndrome (TTP-HUS) is characterized by microangiopathic hemolytic anemia, thrombocytopenia, fever, central nervous system abnormalities, and renal dysfunction. In early reports the mortality approached 100 percent. A treatment protocol was introduced in 1979 for patients admitted to Johns Hopkins Hospital with the diagnosis of TTP-HUS. Treatment regimens included 200 mg of prednisone a day, for patients with minimal symptoms and no central nervous system symptoms, and prednisone plus plasma exchange, for patients with rapid clinical deterioration who did not improve after 48 hours of prednisone alone and for patients presenting with central nervous system symptoms and rapidly declining hematocrit values and platelet counts.

Results. A total of 108 patients were treated, and 91 percent survived. Prednisone alone was judged to be effective in 30 patients with mild TTP-HUS (2 relapses and 2 deaths). Plasma exchange plus prednisone was given to 78 patients with complicated TTP-HUS, resulting in 67 relapses and 8 deaths. Relapses occurred in 22 of 36 patients given maintenance plasma infusions. Neither splenectomy nor treatment with aspirin and dipyridamole was effective in those with a poor response to plasma exchange. None of the 71 patients tested had positive cultures for O157:H7 *Escherichia coli*. Nine percent of the patients were pregnant, and none gave birth to infants with TTP-HUS.

Conclusions. Effective treatment with 91 percent survival is available for patients with TTP-HUS. (N Engl J Med 1991; 325:398-403.)

THROMBOTIC thrombocytopenic purpura was initially described by Moschcowitz in 1924.[1] Years later a similar disease was recognized in young children and designated the hemolytic uremic syndrome by Gasser et al.[2] Today the two disorders are regarded as parts of a spectrum often designated thrombotic thrombocytopenic purpura–hemolytic uremic syndrome (TTP-HUS).[3,4]

In early reports on thrombotic thrombocytopenic purpura the mortality rate was virtually 100 percent. One of the first documented survivors of the disease, described in 1959, was treated with exchange transfusions.[5] A variety of other therapeutic approaches had been tried in an uncontrolled fashion with limited success. Because of the often fulminant and unrelenting rapid progression of the disorder, multiple treatments have often been employed simultaneously, making it difficult to determine which therapy was effective. In 1963 it was suggested that plasma therapy might be beneficial.[6] We report our experience with the treatment of TTP-HUS with corticosteroids and plasmapheresis with plasma replacement in patients admitted to our facility from September 1979 to December 1990. A placebo-controlled study was not done because plasmapheresis is the only form of therapy for TTP-HUS that is acknowledged to be effective.

METHODS

From September 1979 to December 1990 all patients admitted to Johns Hopkins University Hospital who satisfied the following criteria for the diagnosis of TTP-HUS were treated according to a single protocol. The diagnosis was made if the patient had at least four of the following findings: microangiopathic hemolytic anemia with a negative Coombs' test (extensive red-cell fragmentation on the peripheral-blood smear), thrombocytopenia ($<100\times10^9$ platelets per liter [100,000 per cubic millimeter]), central nervous system abnormalities, fever (temperature, >38°C), and renal (urinary tract) dysfunction. In some patients the diagnosis was confirmed by the presence of intravascular hyaline thrombi in biopsy samples of gingival tissue or bone marrow. Blood-cell counts and levels of serum urea nitrogen, creatinine, and lactate dehydrogenase were measured by standard techniques.

Treatment

Therapy was instituted as soon as the diagnosis of TTP-HUS was established. If the patient had minimal symptoms and was free of central nervous system abnormalities (except for mild headache), corticosteroids were given in the form of 200 mg of oral prednisone per day or, if there was evidence of hepatic dysfunction (reduced albumin levels in the presence of adequate nutrition, elevation in hepatic-enzyme levels, abnormal prothrombin time), 200 mg of intravenous prednisolone per day. If the patient had moderate-to-severe symptoms with changes in mental status or other neurologic abnormalities, or there was rapid clinical deterioration, with the hematocrit decreasing below 0.20, the platelet count falling below 10×10^9 per liter (10,000 per cubic millimeter), the serum lactate dehydrogenase level increasing above 600 U per liter, or the creatinine concentration suddenly increasing above 442 μmol per liter (5.0 mg per deciliter), the patient was given 200 mg of prednisolone per day intravenously, and plasmapheresis and plasma exchange (infusion of 65 to 140 ml of fresh-frozen plasma per kilogram of body weight per exchange) were begun once a day. If the hematocrit was below 0.20, the patient was given packed red cells to increase it to 0.20 to 0.25 before plasmapheresis (model 30, Haemonetics, Braintree, Mass.) was begun.

If patients who were initially treated with corticosteroids alone did not show improvement after 48 hours, have any central nervous system abnormalities, or have clinical or laboratory evidence of deterioration during the 48 hours after the initiation of therapy, plasmapheresis and plasma exchange were begun, and corticosteroids were continued at the same dose. In patients who received corticosteroids alone and who showed improvement, with laboratory values recorded for three successive days returning to the near-normal or normal range, the dose of corticosteroids was rapidly reduced to 60 mg per day and then more slowly (by 5 mg per week). In patients who were treated with both corticosteroids and plasmapheresis and plasma exchange, the plasma treatments were discontinued when there was improvement in clinical status and the laboratory values were normal or nearly normal on two successive days.

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At this time fresh-frozen plasma was administered in the following manner: 20 ml per kilogram on day 1–2, 15 ml per kilogram on day 3–4, 10 ml per kilogram on day 5–6, and 5 ml per kilogram on day 7–8; the infusion was then discontinued. The dose of corticosteroids was tapered as described for patients with improvement who received corticosteroids alone.

If during the infusion of fresh-frozen plasma on the tapering schedule or during the tapering of the corticosteroid dose the clinical or laboratory status deteriorated, plasmapheresis and plasma exchange were reinstituted and the dose of steroids was increased to the starting dose. If the patient did not respond to either corticosteroids or the combination treatment, given either initially or after a relapse, consideration was given to treatment with vincristine (1.4 mg per square meter of body-surface area intravenously, not to exceed 2 mg, on days 1, 4, 7, and 10), antiplatelet agents (300 mg of aspirin orally every eight hours plus 100 mg of dipyridamole orally every eight hours), or splenectomy.

A response to treatment was defined as obvious improvement in clinical status accompanied by a statistically significant increase in the hematocrit and the platelet count and a decrease in the serum lactate dehydrogenase level during a 24-hour period, as compared with the preceding 24 hours. A complete response was achieved when the clinical status returned to normal, accompanied by a return of the hematocrit, platelet count, reticulocyte count, serum lactate dehydrogenase level, and renal function to their respective normal ranges.

Descriptive, statistical techniques were employed in the analysis of the data.[7,8] Survival was analyzed according to the method of Kaplan and Meier.[9]

Monitoring

During hospitalization each patient was monitored daily, with determination of clinical status (vital signs and central nervous system status every six to eight hours), hematocrit, white-cell count, platelet count, reticulocyte count, and serum levels of urea nitrogen, creatinine, and lactate dehydrogenase. We also examined a smear of peripheral blood obtained by direct finger puncture of every patient at least once every three days.

After discharge each patient was seen in the outpatient hematology clinic at intervals of one to three weeks until there was complete recovery, with no need for medications, and subsequently every four months for one additional year. All survivors were contacted at the time of the preparation of this article.

Relapse

Relapse was defined as the recurrence of any or all of the following: the initial signs and symptoms, microangiopathic anemia, thrombocytopenia, abrupt or slowly progressive deterioration in clinical status, and abrupt or insidious deterioration in laboratory values.

Results

A total of 108 patients were treated for TTP-HUS during the 11-year observation period. The characteristics of the patients and diagnostic features of this disease process are given in Table 1.

Admission and discharge laboratory data are given in Table 2. The admission and discharge values were compared for each patient, and there were significant differences in the hematocrit, platelet count, and lactate dehydrogenase values ($P<0.001$ for all comparisons). None of the patients had hypertension at presentation, but two became hypertensive later. Although it was not evident from the data analysis of the entire population, three patients (all female) had severe renal damage (serum urea nitrogen levels, 23.2 to 46.4 mmol per liter of urea [65 to 130 mg per deciliter]; creatinine levels, 716 to 1591 μmol per liter [8.1 to 18.0 mg per deciliter]) and were left with residual renal dysfunction (serum urea nitrogen, 12.5 to 17.85 mmol per liter of urea [35 to 50 mg per deciliter]; creatinine, 265 to 601 μmol per liter [3.0 to 6.8 mg per deciliter]). One patient required long-term extracorporeal renal dialysis. The other two patients (with slight hypertension and renal dysfunction) were treated medically. In six additional patients with evidence of renal dysfunction at the time of presentation or relapse, renal function returned to normal at discharge or during follow-up.

Table 1. Characteristics of 108 Patients with TTP-HUS.*

Characteristic	Female Patients (N = 76)	Male Patients (N = 32)	All Patients (N = 108)
Race			
Black	25	5	30
White	51	27	78
Age — yr (range)	38±13 (16–77)	40±14 (17–68)	38±14 (16–77)
Entry criteria†			
% with 4	22	25	23
% with 5	78	75	77

*Plus–minus values are means ±SD.

†Patients had to satisfy at least four of the following entry criteria: microangiopathic hemolytic anemia, thrombocytopenia, central nervous system abnormalities, fever (temperature, >38°C), and renal (urinary tract) disease.

Seventy-one patients had stool and blood samples cultured for enteric infection with verotoxin-producing *Escherichia coli* serotype O157:H7. All had negative cultures.

Relapse

Relapse was common, occurring in 69 of 108 patients (64 percent) (Fig. 1). Eighty-four percent of the relapses occurred within 30 days of diagnosis, more commonly in women. Two months after the diagnosis, an additional 13 percent relapsed. Two other patients, one male and one female, relapsed five years after the initial diagnosis. Among the 36 patients who received plasma infusion as maintenance therapy, 22 (61 percent) relapsed after an initially excellent response. Because of this high rate of failure, the use of plasma infusion alone as maintenance therapy was discontinued in November 1986. Relapse occurred in 2 of the 30 patients (7 percent) who responded to corticosteroids alone. In these two patients relapse occurred abruptly, soon after their initial, excellent response to corticosteroid therapy. Both died within hours of the recognition of relapse and before additional therapy could be initiated. Among the 78 patients who were treated with steroids and plasmapheresis and plasma exchange, relapse occurred in 67 (86 percent).

In the group of 69 patients who relapsed, 72 percent had a single relapse and 28 percent had more than one relapse. One patient, who was incidentally found to be positive for the human immunodeficiency virus (HIV) at presentation, required readmission for each of six relapses occurring within three months of the initial diagnosis.

Treatment

In 30 of the 108 patients (28 percent) corticosteroids were the only form of treatment (Fig. 1). In 24

Table 2. Admission and Discharge Laboratory Data for 108 Patients with TTP-HUS.*

Time of Evaluation	Hematocrit	White Cells	Platelets	Reticulocytes	Serum Lactate Dehydrogenase	Serum Urea Nitrogen	Serum Creatinine
		$\times 10^{-9}$/liter			U/liter	mmol/liter of urea	μmol/liter
Admission							
Female patients	0.21±0.03 (0.13–0.29)	8.51±3.84 (3.00–22.00)	16.50±11.88 (3.00–55.00)	0.12±0.06 (0.03–0.36)	1139±776 (214–3935)	8.93±5.70 (2.49–35.34)	153.80±210.30 (53–1591)
Male patients	0.22±0.03 (0.15–0.28)	8.64±4.18 (2.90–23.00)	22.25±11.86 (4.00–60.00)	0.10±0.04 (0.04–0.21)	913±312 (322–2100)	11.10±8.21 (4.28–46.70)	163.00±118.50 (62–619)
Discharge							
Female patients	0.37±0.02 (0.26–0.44)	7.86±3.09 (3.60–18.00)	248.14±98.60 (11.00–603.00)	0.035±0.026 (0.01–0.18)	206±55 (90–410)	7.49±2.86 (3.57–21.42)	111.00±63.65 (53–433)
Male patients	0.40±0.03 (0.36–0.45)	8.29±2.99 (5.00–18.00)	255.84±61.73 (140.00–378.00)	0.027±0.01 (0.02–0.04)	202±50 (110–310)	9.20±6.10 (4.99–39.20)	131.00±95.50 (53–548)

*Plus–minus values are means ±SD, with ranges given in parentheses.

additional patients, corticosteroids were used initially, but the patients' conditions either did not improve or deteriorated soon after diagnosis, necessitating the institution of plasmapheresis and plasma exchange. In the 30 patients (22 female and 8 male patients) treated with corticosteroids alone, relapse occurred abruptly in 7 percent. In 54 patients (50 percent) the initial treatment consisted of corticosteroids and plasmapheresis and plasma exchange.

The duration of treatment, both the time to response (interval from the institution of treatment to the occurrence of obvious improvement in clinical status and blood-cell counts) and the total length of treatment, was shortest for those receiving corticosteroids alone. These patients responded in 48 to 72 hours, and corticosteroid therapy was discontinued after 11 to 16 weeks of treatment. In most patients after five to seven days of corticosteroids the daily dose was progressively decreased to zero over the ensuing weeks while clinical status, blood-cell counts, and renal function were monitored.

In the patients who were treated with plasmapheresis and plasma exchange — that is, patients who did not respond to treatment with corticosteroids and patients who presented with severe disease, necessitating immediate therapy with corticosteroids and plasmapheresis and plasma exchange — the earliest response was noted after two rounds (one round per 24-hour period) of plasmapheresis and plasma exchange. In one patient the hematocrit, platelet count, and lactate dehydrogenase level had returned to near-normal values after three rounds of treatment. The fewest

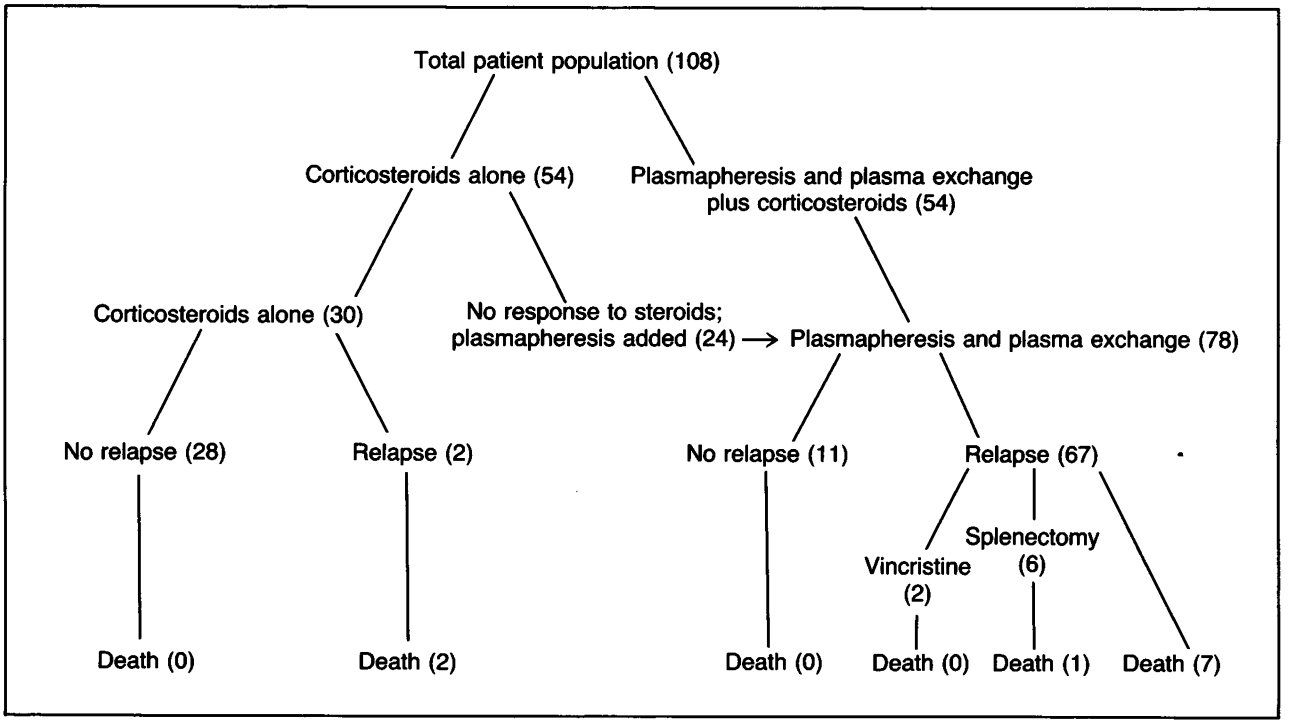

Figure 1. Flow Diagram of the Course of 108 Patients from the Time of Entry into the Study to Treatment and Final Outcome. The numbers in parentheses are the number of patients in each category.

rounds of plasmapheresis and plasma exchange in any patient was 1 round per day on 3 consecutive days, and the greatest number was 27 given at irregular intervals over a period of 41 days. The average number of rounds of plasmapheresis and plasma exchange per patient was nine for female patients and seven for male patients. The average number of units of fresh-frozen plasma per round of plasmapheresis and plasma exchange was 24 (range, 18 to 32).

There were few complications associated with the total of 619 rounds of plasmapheresis and plasma exchange. Two patients had a severe allergic reaction to the plasma. In one patient this was associated with hypotension lasting one to two hours. In the second patient the hypotension resulted in catheter obstruction and clot formation in the centrifuge bowl, and plasmapheresis was discontinued. Three patients had infections of the Shiley catheter and required intravenous antibiotics. Approximately 40 to 45 percent of the patients had minimal-to-mild urticaria, alleviated by premedication with diphenhydramine.

In two female patients the plasma infusion was given concomitantly with corticosteroid therapy. No improvement was noted after 72 hours, and plasmapheresis and plasma exchange were instituted, with good response.

Splenectomy was performed in six patients who did not respond to repeated plasmapheresis and plasma exchange. In each of these patients the postsplenectomy hospital course was extremely complex, with progressive decline in the hematocrit and platelet count and an increase in the serum lactate dehydrogenase level accompanied by deteriorating clinical status. This necessitated the reinstitution of plasmapheresis and plasma exchange, with progressive improvement. One female patient died abruptly in the postoperative recovery unit within hours after uncomplicated splenectomy. Permission for postmortem examination was denied. Relapse occurred within one month in three of the five surviving patients (for a total of seven relapses).

Two female patients received a single course of vincristine therapy because of sustained unresponsiveness to corticosteroids and plasmapheresis and plasma exchange. One patient had four relapses, and the other had six. In both patients after four to five rounds of plasmapheresis and plasma exchange, their clinical status, cell counts, and lactate dehydrogenase levels approached normal. Within four to five days after discontinuation of the plasmapheresis and plasma exchange, however, there was slow but obvious progressive deterioration in clinical status and laboratory measurements. During the next round of plasmapheresis and plasma exchange for the fourth and sixth relapses, respectively, each patient received a course of vincristine. Ten months later neither patient had had another relapse.

Five patients who did not have a sustained response to plasmapheresis and plasma exchange were treated with the antiplatelet agents aspirin and dipyridamole. All five relapsed despite the therapy, and this portion of the protocol was discontinued in 1983.

Nine patients were pregnant and in their third trimester at the time of presentation. Six of these patients had vaginal deliveries and three had cesarean sections. The clinical status and daily blood counts (for 10 days) of the 10 offspring (including one set of nonidentical twins) were completely normal at delivery, during the postpartum period, and at the two-month follow-up. Five of the nine patients subsequently had a normal second pregnancy and delivery.

One patient in this 108-patient population had the rare complication of serous retinal detachment associated with TTP-HUS.[10]

Survival

There were 10 deaths in this series of 108 patients (9 percent) (Fig. 1). Of the patients who died, eight were female and two were male. The overall survival rate was 91 percent (90 percent of the female patients and 94 percent of the male patients). Each survivor was followed for at least one year after clinical and laboratory values had returned to normal. The deaths occurred soon after diagnosis. With one exception, at 16 days, all deaths occurred within 4 days after the diagnosis. Of the 98 survivors, 95 are no longer receiving any medication related to the diagnosis of TTP-HUS. During follow-up one patient had a brief episode of non-A, non-B hepatitis; no one converted from HIV-negative to HIV-positive. The survivors do not have any residual effects or organ damage, and they are able to lead normal lives.

There were no significant differences between female and male patients with respect to the degree of response, rate of response, duration of treatment, magnitude of treatment, or survival rate.

Discussion

For more than 40 years after the initial description of TTP-HUS the mortality rate for this disease was nearly 100 percent.[11,12] In 1963 Bukowski et al. suggested the use of plasmapheresis and replacement with fresh-frozen plasma as a possible treatment for TTP-HUS.[6] Some investigators[13] subsequently suggested that infusion of fresh-frozen plasma was as efficacious as plasmapheresis and plasma exchange. It is now apparent that the infusion of fresh-frozen plasma alone is not efficacious for the majority of patients.[14,15] This is supported by the results of the present study, in which a high frequency of relapse was associated with the infusion of fresh-frozen plasma alone.

Although there has been no controlled, prospective, randomized, appropriately blinded study comparing plasmapheresis and plasma exchange with placebo or with corticosteroid therapy, the observation that some form of plasma therapy is beneficial seems valid. The finding that patient after patient with TTP-HUS who is in coma becomes alert during plasmapheresis and plasma exchange establishes that this is effective ther-

apy. Although there are many possible physiologic or biochemical mechanisms to explain this response,[16] the explanation for its therapeutic success remains unknown.

In the present study and in other published reports, relapse has been observed during treatment with corticosteroids. This raises several questions: Are corticosteroids of any benefit? Should corticosteroids be discontinued during plasmapheresis? Can all the therapeutic benefit be ascribed to some form of plasma therapy? In the literature the majority of patients who have survived this disease received some form of treatment with corticosteroids.[17] In the present study, 28 percent of the patients (30 of 108) responded to corticosteroids alone. It is perhaps important that the rate of relapse in this group was considerably lower than in the patients who required plasmapheresis and plasma exchange. Whether this was because the patients who responded to corticosteroids alone were in an earlier phase of a less severe illness than those who required corticosteroids and plasmapheresis and plasma exchange is unknown. Our results suggest that it is reasonable to employ corticosteroids in the initial treatment of this illness.

Six patients underwent splenectomy because of refractoriness to the combination of corticosteroids and plasmapheresis and plasma exchange.[18,19] There are no established guidelines for the duration or frequency of plasmapheresis and plasma exchange.[20] It is possible that persistent plasma therapy may have obviated the need for splenectomy. All six patients who underwent splenectomy had a pronounced deterioration in clinical status and a decrease in peripheral-blood counts immediately after splenectomy: four patients became comatose, and one died abruptly. Five of the six patients survived and regained their health. Since the one instance of sudden death within hours of splenectomy in 1984, we have not performed the procedure for this disease.

Since the rate of response was 0 percent in those who received antiplatelet therapy, we have not administered this therapy since 1983. If these patients do have a platelet-aggregating factor in plasma,[16] known antiplatelet agents have no inhibitory effect against this agonist.[21] At present there is little evidence to support the use of antiplatelet agents in the treatment of this disease.[22-26]

Eleven patients were referred because they had a precipitous decline in clinical status after a transfusion of platelets. In nine of these patients there was an abrupt, striking deterioration in clinical status and an increase in the frequency of hemorrhage and renal failure, with the mean serum creatinine concentration increasing from 97.24 μmol per liter (1.1 mg per deciliter) (range, 53.04 to 123.76 [0.6 to 1.4]) to 680.68 μmol per liter (7.7 mg per deciliter) (range, 459.68 to 822.12 [5.2 to 9.3]) in less than 24 hours. This experience has been observed by others.[17,27-29] We refrain from administering platelets to patients with TTP-HUS. The mechanism whereby the transfused platelets, possibly in combination with unusually high levels of von Willebrand multimers,[30-33] induce organ dysfunction has not been elucidated.

Relapse after the apparent induction of remission was observed in 69 of the 108 patients, for a frequency of 64 percent. Relapse occurred most often in the first month, but two patients relapsed five years after the initial diagnosis. Some investigators[34] have regarded relapse as an unusual and rare event in this disease. The number of relapses in our study ranged from one to six in a given patient. The patient with the highest number of relapses, six in three months, was unaware that she was positive for HIV, a finding that was discovered incidentally at the time of the initial plasmapheresis. The only other HIV-positive patient (in whom the diagnosis was made 11 months before that of TTP-HUS) had a single relapse. The possibility that HIV causes TTP-HUS has been considered.[35-41] In the present study, 2 of the 62 patients tested were HIV-positive. Thus, compelling support for an etiologic association is lacking.

From the present study it is evident that the infusion of plasma, treatment with antiplatelet agents, corticosteroid therapy, and splenectomy do not prevent relapse. The following questions must be raised: Was therapy discontinued prematurely, and can relapse be prevented by daily plasmapheresis and plasma exchange for a fixed number of days? Would this prevent recurrent relapse? Would the results be different if larger volumes of fresh-frozen plasma were used for plasmapheresis and plasma exchange or if the infusion were given twice instead of once a day?

To guide the decision to discontinue plasmapheresis and plasma exchange, we monitored the clinical status, hematocrit, reticulocyte count, platelet count, and serum lactate dehydrogenase level daily. Red-cell morphology was examined every third day. As these values approach normal and once the lactate dehydrogenase level falls below 400 U per liter on two consecutive days, it is our present routine to discontinue plasmapheresis and plasma exchange and to taper the dose of steroids slowly.

The survival rate in the present study is considerably different from that observed in the 1970s. It is apparent that excellent treatment for TTP-HUS is now available. This treatment is demanding; requires a large number of professional personnel, a huge number of blood donors (an average of 215 donors per patient; one patient required 675 donors), and expensive equipment; and has a potential risk of disease transmission.

Recently, the use of high-dose intravenous immune globulin has been reported in the treatment of this illness.[42-53] It was not used in our study but deserves investigation, as does the use of vincristine.[54]

At least three important factors contribute to the improvement in survival among patients with TTP-HUS: earlier recognition and diagnosis, progressive improvement in general medical care and facilities, and plasma therapy. Simpler treatment that is more readily available is needed. Although potentially valuable clues have emerged,[16] the most important need is to discover the cause of this devastating disease.

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