Complications of plasma exchange in 71 consecutive patients treated for clinically suspected thrombotic thrombocytopenic purpura–hemolytic-uremic syndrome

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BACKGROUND: With the increased frequency of diagnosis and improved survival of thrombotic thrombocytopenic purpura–hemolytic-uremic syndrome (TTP-HUS), the morbidity of plasma exchange (PE) treatment has become more important.

STUDY DESIGN AND METHODS: Data were prospectively collected on 71 consecutive patients referred to the Oklahoma Blood Institute (OBI) for PE treatment for clinically suspected TTP-HUS from mid-1996 to mid-1999. Complications were defined as major or minor, and distinguished between those related to central venous catheter access or to the plasma.

RESULTS: Twenty-one patients (30%) had 27 major complications, which caused two deaths. The major complications included 2 episodes of hemorrhage after subclavian line insertion (1 death), 1 pneumothorax requiring a chest tube, 12 systemic infections (1 death), 7 episodes of catheter thrombosis requiring removal of the central venous catheter, 2 episodes of venous thrombosis requiring anticoagulant treatment, 2 episodes of hypoxemia and hypotension, and 1 episode of serum sickness. Minor complications occurred in 22 additional patients (31%). Twenty-eight patients (39%) had no complications.

CONCLUSIONS: The morbidity and mortality of catheter placement and PE are important considerations when PE treatment for clinically suspected TTP-HUS is anticipated.

Thrombotic thrombocytopenic purpura–hemolytic-uremic syndrome (TTP-HUS) was fatal in 90 percent of patients[1] until the use of plasma exchange (PE) therapy began in the 1970s. Treatment with PE decreased mortality to 18 percent in 12 case series,[2] and this resulted in a dramatic change in the clinical approach to diagnosis and management. With the availability of potentially curative PE, the decision to begin treatment has become urgent, and because of that urgency, diagnostic criteria have become less stringent.[3] With these less stringent criteria, the frequency of diagnosis and treatment of TTP-HUS has increased dramatically.[4] Many acutely ill patients have signs and symptoms suggesting TTP-HUS; when an alternative cause is not clearly present, a decision must be made regarding central venous catheter placement and PE. An understanding of the risks of these procedures is important for this decision.

Large studies describing adverse events associated with apheresis and PE have reported few major complications.[5-8] However, these data may not accurately describe the risks for patients with TTP-HUS, because many patients in these reports were not acutely ill and required few procedures, and most did not undergo plasma replacement. Three studies documented the diagnosis of reported patients: the number of patients with TTP-HUS was 17 of 181 patients,[5] 49 of 627 patients,[6] and 2 of 50 patients.[7] Patients with TTP-HUS had a higher frequency of adverse events in one report[6]; in

ABBREVIATIONS: OBI = Oklahoma Blood Institute; PE = plasma exchange; TTP-HUS = thrombotic thrombocytopenic purpura–hemolytic-uremic syndrome.

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another study, all five major complications occurred in one patient with TTP-HUS[7]; and the third study did not describe complications related to specific diagnoses.[5] One reason to suspect a greater risk for complications in patients with TTP-HUS is that patients requiring plasma replacement have more complications than patients who undergo colloid replacement.[6-8] Moreover, central venous catheter-related complications may be more frequent in patients with TTP-HUS, because they require more PE treatments than patients with other diseases.[4] Catheter-related complications were not systematically described in the two largest studies.[6,8]

To define more clearly the risks of PE in patients treated for clinically suspected TTP-HUS, we report the complications occurring in 71 consecutive patients.

MATERIALS AND METHODS

Patients

The study population consisted of all patients referred to the Oklahoma Blood Institute (OBI, Oklahoma City, OK) from June 25, 1996, to June 25, 1999, for PE treatment of clinically suspected TTP-HUS. The OBI does all the PE procedures for central and western Oklahoma; therefore, all patients in our region with clinically suspected TTP-HUS for whom PE was ordered are included in this case series. During this time, 76 patients were referred to the OBI for PE for their first episode of clinically suspected TTP-HUS; 3 died before PE could be initiated, 1 recovered without PE, and 1, with advanced cancer and mitomycin C-induced TTP-HUS, was not treated. The remaining 71 patients were treated with PE until recovery or death, or until an alternative diagnosis (e.g., unexpected malignant or infectious disease) became apparent.

All 71 patients fulfilled the diagnostic criteria for TTP-HUS (thrombocytopenia and microangiopathic hemolytic anemia)[3]; most patients also had neurologic (78%) and renal (92%) abnormalities, and 49 percent of patients had fever. However, the diagnostic dilemma of TTP-HUS is emphasized by the observation that in 27 (38%) of these patients, there were alternative or additional explanations for these abnormalities, which often were not apparent at presentation. In 5 patients, unsuspected malignancy was discovered; in 4, sepsis was subsequently diagnosed; and in 6 patients (2 patients each), HIV infection, malignant hypertension, and heparin-induced thrombocytopenia thrombosis may have caused the abnormalities. Twelve patients had clinically apparent autoimmune disease, but TTP-HUS was considered an appropriate additional diagnosis that required PE.

This report focuses on the initial episode of TTP-HUS, because the risks of PE, which play a role in treatment decisions for patients with an initial and sometimes uncertain diagnosis of TTP-HUS, are not relevant for patients with recurrent disease who require immediate PE. Moreover, the complication rates may be greater in patients who require multiple courses of treatment. Therefore, data on eight patients who had 12 recurrent episodes during this time are analyzed separately.

PE procedure

Central venous catheters were required for vascular access in 68 (96%) of 71 patients. Percutaneous catheters were inserted at the bedside by direct venipuncture into a femoral, subclavian, or internal jugular vein. Femoral catheters were typically used in more acutely ill patients with more profound thrombocytopenia. Tunneled subclavian or internal jugular catheters were placed when an operating room or interventional radiology procedure was feasible. There was no standard protocol for catheter insertion. Between procedures, catheters were filled with heparin at 1000 to 5000 units per L. Procedures were performed with an apheresis machine (LW-9000 MCS+, Haemonetics, Boston, MA); each procedure replaced 1 calculated plasma volume. Both FFP and the cryosupernatant fraction of plasma (CPP) were used as replacement fluid; S/D-treated plasma was not used. All data were collected by the OBI staff at the time of each procedure and recorded on a form prepared specifically for this study.

Complications

Complications were distinguished as those related to the central venous catheter access and those related to the plasma infusion (Table 1). Complications were defined as major by criteria similar to those described by Ziselman et al.[5]; complications caused by the venous access or the PE procedure that did not meet these criteria were defined as minor (Table 2).

RESULTS

During the 3-year study period, 71 patients were treated with PE at 11 hospitals for their initial episode of clinically

TABLE 1. Classification of PE complications: central venous catheter access-related complications and plasma-related complications

Catheter-related	Plasma-related
Insertion procedure	Allergic
Pneumothorax	Hypoxemia
Hemorrhage	Hypotension
	Seizure
Infection	Serum sickness
Systemic infection	Urticaria
Bacteremia	
Fungemia	Alkalosis
Local infection at catheter site	Tetany
	Nausea, vomiting, diarrhea
Thrombosis	
Venous thrombosis	Volume depletion
Catheter obstruction	Hypotension
	Syncope, seizure
	Infection
	Transfusion-transmitted virus

suspected TTP-HUS. The mean age of these patients was 50 years (range, 14-85 years), and 70 percent were female. The mean number of PE procedures per patient was 12 (range, 1-71); the total number of PE procedures was 884. FFP was used in 574 procedures (65%) and CPP in 310 (35%). Ten patients required twice-daily PE for 1 to 11 days for severe manifestations of TTP-HUS that was uncontrolled by once-daily PE. Three of the 71 patients were diagnosed after allogeneic BMT and were receiving multiple immunosuppressive agents. Of the remaining 68 patients, 41 (60%) were treated with glucocorticoids (principally for the diagnosis of TTP-HUS), 9 were treated with cyclophosphamide (8 for concurrent autoimmune disease), 2 with vincristine (1 for concurrent autoimmune disease), and 2 with splenectomy.

In 3 patients, the course of PE was successfully completed with peripheral venipuncture. The remaining 68 patients required 92 central venous catheters for vascular access, an average of 1.4 catheters per patient: 27 percutaneous femoral catheters, 39 percutaneous subclavian or internal jugular catheters, and 26 tunneled subclavian or internal jugular catheters. The mean length of time that these catheters were maintained was 6.6 days (range, 2-19; SD 4.0) for femoral catheters, 14.9 days (range, 1-56; SD 12.1) for percutaneous subclavian or internal jugular catheters, and 34.0 days (range, 5-120; SD 29.5) for tunneled subclavian or internal jugular catheters. The total number of patient-catheter days was 1646.

TABLE 2. Classification of PE complications: definition of major complications

Prevention of the performance or completion of the PE procedure
Systemic infection, documented by positive blood cultures or treated presumptively with a complete course of an antimicrobial agent
Requirement for hospitalization if procedure was performed on an outpatient basis, or transfer to an intensive care unit, or prolongation of hospitalization
Requirement for an invasive procedure (e.g., chest tube, replacement of the central venous catheter)
Requirement for RBC transfusion
Requirement for systemic treatment other than diphenhydramine, hydrocortisone, or $CaCl_2$

Twenty-one (30%) of 71 patients (95% CI, 19-42%) had 27 major complications that resulted in two deaths. No other deaths were directly attributable to complications of PE. Twenty-two additional patients (31%) had one or more minor complications. Major complications did not occur more often in more severely ill patients: 6 (29%) of the 21 patients with major complications died, as did 16 (32%) of the other 50 patients. Major complications occurred in 10 of 11 hospitals and were not clustered in any hospital. The one hospital with no major complications treated only 2 of the 71 patients. Minor complications occurred in all 11 hospitals.

Major catheter-related complications (Table 3) occurred in one patient, a 28-year-old woman who was 5 days postpartum and who died suddenly of hemorrhage after elective insertion of a percutaneous subclavian catheter to replace an initial femoral catheter, when her platelet count was 83,000 per µL. Her hemorrhage was related in part to systemic lupus erythematosus with recurrent pleuritis and pericarditis that had been treated continually with glucocorticoids for 9 years. One other patient had bleeding at the catheter insertion site that prevented treatment, when her platelet count was 75,000 per µL. No other hemorrhage occurred that required RBC transfusion or prevented treatment, despite 18 catheter insertions in 17 patients whose platelet counts were <20,000 per µL and 31 catheter insertions in 29 patients whose platelet counts were 20,000 to 50,000 per µL. Platelet transfusions were given with no apparent adverse effect before 7 of the 18 catheter insertions in patients with platelet counts <20,000 per µL.

Ten episodes of bacteremia and two episodes of fungemia, resulting in one death, were documented in 11 patients (Table 4). The frequency of sepsis was similar with all catheter types (femoral, 3/27 [11%]; percutaneous subclavian/internal jugular, 5/39 [13%]; tunneled subclavian/internal jugular, 4/26 [15%]). The rate of sepsis per 1000 patient-catheter days was 7.3. None of the episodes of sepsis was preceded by obstruction of the catheter. In most patients, sepsis occurred soon after catheter insertion. Table 4 also documents that most patients had multiple, complex problems and treatments, including the one patient who died of infection. Patients 10 and 11 became infected while at home, probably because of their poor hygiene and IV drug abuse; Patient 11 had a positive urine test for cocaine when he was admitted for *Escherichia coli* bacteremia. None of the three patients treated for suspected TTP-HUS after allogeneic BMT, who were perhaps the most complicated patients, had infectious (or any other major or minor) complications.

TABLE 3. Major complications related to central venous catheters

	Number of complications for types of catheters		
		Subclavian/internal jugular	
Complication	Femoral	Percutaneous	Tunneled
Catheter insertion			
Pneumothorax requiring chest tube		1	
Hemorrhage			
Requiring transfusion		1	
Preventing PE			1
Infection			
Bacteremia documented	2	5	3
Fungemia documented	1		1
Thrombosis			
Venous thrombosis requiring anticoagulation	1		1
Catheter obstruction requiring removal of catheter	4	1	2

TABLE 4. Characteristics of patients with catheter-related bacteremia or fungemia

Patient	Catheter type*	Days after insertion	Organism from blood culture	Comorbidity (other treatments)†
1	IJ (T)	34‡	*Serratia marcesens*	Wegener's granulomatosis (P, C)
2	IJ (T)	3	*Staphylococcus aureus*	None
3	SC (P)	4	*Enterococcus*	COPD, recent resection of lung cancer, admission for pneumonia 8 days before PE was begun for TTP-HUS
4	IJ (T)	17	*S. aureus*	None (P)
5	Fem (P)	3	*S. aureus*	SLE (P)
6	SC (P)	3	*S. aureus*	HIV infection
7	IJ (T)	1	*S. aureus*	None
8§	Fem (P)	8	*Enterococcus*	SLE (P, C)
		13	*Candida albicans*	
9	IJ (T)	10	*C. albicans*	18 days after heart surgery, chest tubes for loculated effusions
10	IJ (T)	11	*S. epidermidis*	Chronic renal failure, poor hygeine
11	IJ (T)	12	*E. coli*	HIV infection, IV cocaine abuse

* IJ, internal jugular vein; SC, subclavian vein; Fem, femoral vein; (T), tunneled; (P), percutaneous.
† COPD, chronic obstructive pulmonary disease; SLE, systemic lupus erythematosus; Other treatments: P, prednisone; C, cyclophosphamide.
‡ This catheter had been inserted for hemodialysis; sepsis occurred on the first day of PE. All other catheters were inserted for PE treatment of clinically suspected TTP-HUS.
§ This patient had two episodes of sepsis while the same femoral catheter was in place.

Three plasma-related major complications occurred. Two patients developed concurrent hypotension and hypoxemia, presumably caused by an allergic reaction to the plasma: one patient required transfer to an intensive care unit, and the reaction in the other patient prevented the PE procedure from being completed. One patient developed acute polyarthritis, resembling serum sickness, and required treatment with prednisone for 5 weeks. These complications occurred with the use of both FFP and CPP.

Minor complications occurred in 22 additional patients (31%), as well as in some patients who also had major complications. These included urticaria (22 patients), hypotension or hypoxia (9 patients), catheter obstruction that did not prevent completion of PE (8 patients), local infections at the catheter exit site (7 patients other than those with bacteremia or fungemia), tetany or diarrhea due to citrate toxicity (3 patients), minor hemorrhage at the insertion site (2 patients), and transient hypotension with a seizure presumably due to hypovolemia (1 patient). No transfusion-transmitted infections were documented.

During the 3 years of this study, eight patients had 12 episodes of recurrent TTP-HUS (their second, third, or fourth episodes). There were five major complications in two of these patients. One patient had three episodes of bacteremia and one occurrence of catheter obstruction that prevented completion of PE. The total number of patient-catheter days for these 12 episodes was 404; the rate of sepsis per 1000 patient-catheter days was 7.4. The other patient with major complications, a 59-year-old woman, had a fatal myocardial infarction during PE treatment: sudden death occurred during the 63rd PE administered for her second episode of TTP-HUS, when her disease was apparently controlled (platelet count, 181,000/μL; Hct, 32%; LDH, 205 U/L), but prompt exacerbations had occurred with previous attempts to discontinue treatment. Autopsy revealed an acute septal infarct superimposed on a recent infarct, which probably had occurred at the onset of this episode of TTP-HUS, 11 weeks earlier.

DISCUSSION

Patients who are acutely ill with microangiopathic hemolytic anemia, thrombocytopenia, renal failure, and neurologic symptoms of uncertain etiology are not uncommon. In these patients, the diagnosis of TTP-HUS and treatment with PE may be considered. The decision regarding PE treatment often involves a comparison of the risk of withholding a potentially life-saving treatment and the risk of initiating treatment. Because four large studies have reported that PE treatment is relatively safe,[5-8] it often seems prudent to proceed with that treatment.

The previous data on complications of PE[5-8] do not, however, directly address the risks in patients with clinically suspected TTP-HUS. These patients may be more critically ill than most patients described in previous series[5-8]; many have multiple medical problems and treatments, such as those described for the patients in this report with bacteremia and fungemia (Table 4). The severity of illness among our patients is emphasized by the 31 percent mortality. The mortality among our patients may be higher than that reported in other series,[2] because of our inclusion of patients with alternative or additional diagnoses, who are often critically ill.

Therefore, we documented the complications of PE treatment in 71 consecutive patients treated for their initial episode of clinically suspected TTP-HUS. The morbidity was great: 21 patients (30%) had 27 major complications, resulting in two deaths. We separately analyzed the data from 8 patients with 12 episodes of recurrent TTP-HUS, anticipating that the frequency of complications in them

may be greater. However, the occurrence of major complications was similar (25%, 1 death) to that in the 71 patients being treated for their initial episode. These data should be generalizable to routine clinical practice, as they are from all patients with clinically suspected TTP-HUS in central and western Oklahoma, and they represent the practice of 11 different hospitals.

Clinically significant bleeding related to central venous catheter insertion occurred in only two patients, one of whom died of hemorrhage caused in part by complications from systemic lupus erythematosus and prolonged, continuous glucocorticoid treatment. Although bleeding may be expected in these severely thrombocytopenic patients, our experience is consistent with other studies reporting only rare and minor bleeding complications from central venous catheter placement in patients with hemostatic abnormalities.[9,10] In 10 patients, 11 central venous catheters were inserted when the platelet count was <20,000 per µL, without platelet transfusions and without bleeding complications. Seven other patients with platelet counts <20,000 per µL received a platelet transfusion before catheter insertion, with no apparent adverse effects (although complications of platelet transfusions are reported in TTP-HUS[11]) or excessive bleeding.

Twelve episodes of bacteremia or fungemia occurred in 11 patients. This was the most frequent major complication, occurring in 17 percent of patients; it accounted for 44 percent of all major complications and resulted in one death. Although previous studies have documented more bloodstream infections with femoral catheters than with subclavian catheters[12] and with percutaneous catheters than with tunneled central venous catheters,[13] the rates of infection in our patients were similar for all catheter locations and types. Other factors, including comorbidities (Table 4), seemed more relevant to the risk for sepsis among our patients. The occurrence of sepsis within 4 days after catheter insertion in five patients (Table 4) suggested problems with aseptic technique. In two patients, sepsis seemed related to poor home management of the catheter. However, the rate of bacteremia and fungemia in our patients, 7.3 per 1000 patient-catheter days, was the same as in other reports of bacteremia and fungemia in patients with central venous catheters (4-13/1000 patient-catheter days[14]). The use of catheters impregnated with antimicrobial and/or antiseptic agents[14,15] may decrease the rate of catheter-related bacteremia and fungemia, but these agents are not yet universally recommended[16] and are not yet used in our community.

Minor allergic reactions to plasma, manifested by urticaria, are common, easily controlled, and subsequently prevented by the use of diphenhydramine and hydrocortisone. Acute severe allergic reactions, manifested by hypotension and hypoxemia, occurred in 2 (3%) of our patients. Neither patient had sequelae from these reactions, such as the syndrome of transfusion-related acute lung injury described with PE treatment for TTP-HUS.[17] S/D-treated plasma has been recommended for patients with TTP-HUS,[18] because it can decrease the risk of infection with lipid-enveloped viruses, but this was not a complication among our patients. S/D-treated plasma offers no advantage for diminishing the risk of allergic reactions.[18]

Among the major complications documented in this study, the potentially avoidable complications are due to catheter placement and catheter-related infection and thrombosis. The effort to avoid these complications must be intensified. Aseptic technique during catheter placement appeared to be a greater risk factor among our patients than the type or location of the catheter (Table 4), and therefore greater emphasis on aseptic technique is required. Moreover, the use of antimicrobial-impregnated catheters should be considered,[14,15] and strict protocols should be followed for catheter maintenance, including patient instruction on proper catheter care. Catheters should be removed as soon as possible, but this decision is difficult, because prompt exacerbation of TTP-HUS when PE is stopped is frequent.[11] Therefore, the benefit of removing the central venous catheter must be balanced against the risks of placing a new catheter if further PE treatment is required.

These data are important to inform physicians and patients about the risks of PE for patients with clinically suspected TTP-HUS, which are greater than reported for all patients treated with apheresis and PE.[5-8] Although these risks must be accepted for patients in whom the diagnosis of TTP-HUS seems certain, for patients in whom such a diagnosis is less certain, the potential benefits of a therapeutic trial of PE must be balanced against the high frequency of major complications.

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