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Lessons Learned from the Oklahoma Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome Registry

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The Oklahoma TTP-HUS Registry provides a complete community perspective of thrombotic thrombocytopenic purpura (TTP). This is possible because plasma exchange is the essential treatment for TTP and the Oklahoma Blood Institute provides all plasma exchange procedures for a region encompassing most of the State, including 58 of Oklahoma's 77 counties. The Registry is an inception cohort of consecutive patients for whom plasma exchange treatment was requested for a diagnosis of either TTP or hemolytic uremic syndrome (HUS). All 382 patients identified from January 1, 1989 to December 31, 2007 have consented to be enrolled. Complete follow-up is available for 380 of 382 patients. Patients are described both by clinical categories, related to their associated conditions and clinically apparent etiologies, and by the presence of severe ADAMTS13 deficiency. ADAMTS13 activity has been measured on 235 (93%) of 254 patients since 1995. Registry data have provided new perspectives on the definition and diagnoses of these syndromes as well as their outcomes. Long-term follow-up has documented that relapse is common among patients with ADAMTS13 deficiency but rarely occurs in patients without ADAMTS13 deficiency. Long-term follow-up has also documented persistent abnormalities of health-related quality-of-life and cognitive function. In addition to providing new perspectives on the natural history of these syndromes, The Oklahoma TTP-HUS Registry provides a support group for our patients, information about evaluation and management for community physicians, and a resource for research and educational programs. J. Clin. Apheresis 23:129–137, 2008.

Key words: plasma exchange; ADAMTS13; pregnancy; quinine

INTRODUCTION

Since its inception in 1989, The Oklahoma Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome (TTP-HUS) Registry has become an established service to the community and resource for education [1,2]. The goal of this report is to describe how the Registry began, how it functions, and the lessons we have learned from documentation of the complete community experience with these uncommon syndromes.

METHODS

The Oklahoma TTP-HUS Registry is possible because (1) plasma exchange treatment is the standard care in our region for adults with either TTP or HUS, for children with TTP, and for some children with HUS and (2) the Oklahoma Blood Institute (OBI) is the sole provider of plasma exchange services for all hospitals in 58 of the 77 counties in the State of Oklahoma, a region with a population of 2,310,000 in 2000 [3]. Therefore, the Registry enrolls all consecutive patients within a defined region in whom the diagnosis of TTP or HUS is established and a decision to initiate plasma exchange treatment is made [1,4]. The patients enrolled in the Registry are an inception cohort, identified at the time of their diagnosis with TTP or HUS, a uniform point in their clinical course. Although some children with diarrhea-associated HUS and severe neurologic abnormalities are also treated with plasma exchange, most children with diarrhea-associated HUS are treated only with supportive care and therefore are not included in the Registry. The Oklahoma TTP-HUS Registry is approved by the Institutional Review Boards of the University of Oklahoma Health Sciences Center and each participating hospital.

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TABLE I. Clinical Categories of 382 Patients in the Oklahoma TTP-HUS Registry, 1989-2007

Category	Patients >10-years old	Patients <10-years old
Clinically diagnosed patients (Diagnosed at initial episode)		
Allogeneic stem cell transplant	23	0
Pregnant/postpartum	26	0
Drug-associated	47	0
Acute (immune-mediated)	27	0
Chronic (dose-dependent toxicity)	20	0
Bloody diarrhea prodrome	23	4
Additional or alternative disorder	97	2
Autoimmune disorder	39	1
Sepsis	27	0
Cancer	12	0
Multi-organ failure	10	0
HIV infection	6	0
Malignant hypertension	3	0
Congenital hemolytic anemia	0	1
Idiopathic	136	4
Total	**352**	**10**
Clinically diagnosed patients (Diagnosed at 2nd or later episode)	8	0
Patients diagnosed by renal biopsy	12	0
Total patients	**372**	**10**

Patients are assigned in a hierarchical, sequential order to one of six clinical categories related to associated conditions and potential etiologies that were clinically apparent during their initial episode [4]: (1) Following hematopoietic stem cell transplantation (HSCT), (2) pregnant/postpartum, (3) drug association, (4) bloody diarrhea prodrome, (5) presence of an additional or alternative disorder which may have caused the presenting features, and (6) idiopathic, if none of the criteria for the previous five clinical categories were fulfilled (Table I). Demographic, clinical, and laboratory data are collected prospectively in a Microsoft Access® database [4]. Serum for ADAMTS13 assays has been collected immediately before the first plasma exchange procedure beginning on November 13, 1995. Since that time samples have been obtained on 235 (93%) of 254 patients. ADAMTS13 activity is measured by our research collaborators, Drs. Johanna A. Kremer Hovinga and Bernhard Lämmle of the University of Bern, Switzerland, using two methods, the quantitative immunoblotting of proteolyzed von Willebrand factor multimers [5,6] and a fluorogenic assay using the FRETS-VWF73 substrate [7,8].

RESULTS AND DISCUSSION

History

In 1993, we began a project to document the outcomes of patients with TTP in Oklahoma City with the goal of establishing a community standard of care. We soon recognized the unique opportunity to identify all patients with TTP throughout most of the State because in this region the OBI is the sole provider of plasma exchange services. Complete records of all patients treated with plasma exchange for a diagnosis of TTP or HUS were available from January 1, 1989; therefore this date was established as the beginning of the Registry. Data were then collected from OBI and hospital records for all patients treated with plasma exchange for a diagnosis of TTP or HUS since January 1, 1989 and follow-up of the surviving patients was begun. Since 1994 all data have been collected prospectively because we are notified by the OBI at the time of each request for plasma exchange for a diagnosis of TTP or HUS. Often we are also notified directly by the treating physician because of their awareness of the Registry and of our interest in the evaluation, management, and follow-up of patients with TTP and HUS.

Only 4 patients were treated with plasma exchange for TTP or HUS in 1989; 7 were treated in 1990, and the number of patients increased steadily through 1995. For the past 13 years, 1995 to 2007, an average of 23 patients have been enrolled each year. This experience is parallel to the experience of the Canadian Apheresis Group that reported a 10-fold increase in the annual number of patients treated for TTP with plasma exchange, 1984 to 1997, [9] attributed to greater awareness of TTP following publication of the clinical trial documenting the effectiveness of plasma exchange treatment [10].

Patients

Over 19 years, from January 1, 1989 through December 31, 2007, the Registry has enrolled 382 patients. As consent to enroll in the Registry provides additional information and support with no change of management, no patients have declined to participate. Of the 382 patients, 362 were diagnosed with their initial episode by clinical criteria, 12 were diagnosed with their initial episode by a renal biopsy documenting thrombotic microangiopathy (TMA), and 8 patients were enrolled at the time of a relapse because their initial episodes had occurred before 1989 or outside of the Registry region (Table I). Patients with a renal biopsy diagnosis, rather than a clinical diagnosis, are analyzed separately because (1) some of these patients did not fulfill the clinical diagnostic criteria of thrombocytopenia and microangiopathic hemolytic anemia and (2) plasma exchange treatment may not be requested for all patients with a pathological diagnosis of renal TMA. Consistency of evaluation is provided by one of the authors (J. N. G.) who has seen 283 (91%) of the 312 patients enrolled during their initial episodes since January 1995. Complete patient follow-up is a principal goal of the Registry, because long-

term outcomes are still not well defined for TTP and HUS. Follow-up is currently complete on 380 of the 382 Registry patients.

Our system of clinical categories related to associated conditions and potential etiologies that were clinically apparent during the initial episode (Table I) was established before the discovery of the role of ADAMTS13 in the pathogenesis of TTP. These clinical categories continue to guide our evaluation and management and continue to have value for estimating prognosis. The category of additional or alternative disorders is complex. For example, TTP may occur in patients with a preexisting autoimmune disorder, such as systemic lupus erythematosus (SLE); in these patients we consider that SLE is an additional disorder. In patients who begin plasma exchange treatment for a diagnosis of TTP and then another diagnosis is subsequently discovered that can explain their clinical features, plasma exchange is stopped and the alternative diagnosis is recorded as the definitive diagnosis. In some patients, the alternative diagnosis is not discovered until autopsy examination [11]. However, because there is no way to definitively exclude the diagnosis of TTP, all patients are retained in the Registry and surviving patients are followed to confirm the definitive diagnostic decision.

Only 10 (3%) of 382 Registry patients have been children less than 10-years old (Table I), consistent with observations that TTP and HUS syndromes other than diarrhea-associated HUS are rare in young children and that plasma exchange is not standard treatment for diarrhea-associated HUS. There are no children less than 10-years old among the clinical categories of stem cell transplant, pregnancy, and drug-associated syndromes. Four had diarrhea-associated HUS with acute renal failure, the most common syndrome among children; plasma exchange was requested because of severe neurologic abnormalities or atypical features. Three of the four children in the idiopathic category also had acute renal failure but did not have a diarrhea prodrome and therefore were characterized as atypical HUS; the other idiopathic patient had severe ADAMTS13 deficiency and has had two relapses, similar to adults with TTP and severe ADAMTS13 deficiency. In two children the diagnosis was changed following an initial diagnosis of TTP. The infant in the category of autoimmune disorders was determined to have immune thrombocytopenic purpura with anemia due to persistent, severe hemorrhage. Another child was determined to have congenital hemolytic anemia with marked red cell morphologic abnormalities; thrombocytopenia was attributed to splenomegaly (Table I).

Demographics

Because all patients within a defined geographic region for whom plasma exchange treatment is requested for a diagnosis of TTP or HUS are identified, we can describe the demographics of these syndromes. The age-sex-race standardized annual incidence rates are 11.3 per 10^6 population for all Registry patients and 1.7 per 10^6 population for patients with ADAMTS13 activity less than 5% [12]. Remarkable gender and racial disparities were documented. Among the patients with ADAMTS13 deficiency, the standardized relative incidence rate ratio for blacks to non-blacks was 9.3 and for women to men was 2.7 [12].

TABLE II. Nomenclature for Syndromes that Fulfill the Diagnostic Criteria of Thrombocytopenia, Microangiopathic Hemolytic Anemia, and No Alternative Etiology

Syndrome name	Patients included
TTP	All adults (with few exceptions) Children without acute renal failure
HUS	Children with acute renal failure and a diarrhea prodrome (typical diarrhea-associated HUS) Children with acute renal failure but no diarrhea prodrome (atypical HUS)
TMA	Pathologic term that describes multiple disorders in addition to TTP and HUS, such as malignant hypertension; manifestations are often limited to the kidney Adults or children following allogeneic hematopoietic stem cell transplantation

Definitions

The variety of presentations and associated conditions (Table I) emphasize the heterogeneity of these syndromes; heterogeneity of clinical syndromes may cause confusion about definitions and nomenclature. The names applied to these syndromes, TTP or HUS, are important because they can influence management decisions. The standard of care for patients with TTP is plasma exchange and therefore use of the term TTP requires consideration of plasma exchange treatment. TTP is defined by diagnostic criteria established by the Canadian Apheresis Group for their clinical trial that documented the effectiveness of plasma exchange treatment [10]: (1) thrombocytopenia, (2) microangiopathic hemolytic anemia, and (3) no alternative etiology.

TTP is the term we use to describe all adult patients who fulfill these criteria, whether or not they have neurologic abnormalities or renal failure, and whether or not they have severe ADAMTS13 deficiency (Table II). Plasma exchange is appropriate treatment for all adults who fulfill these diagnostic criteria, including patients with renal failure [13].

HUS is the term we use for children who have a diarrhea prodrome and renal failure in addition to thrombocytopenia and microangiopathic hemolytic anemia (Table II). Since the standard management for these

children is supportive care without plasma exchange [14,15], a diagnosis of HUS in any patient may suggest withholding plasma exchange treatment. Since we consider plasma exchange to be appropriate treatment for all adults who fulfill the diagnostic criteria of thrombocytopenia and microangiopathic hemolytic anemia with no alternative etiology, we do not use the term HUS for adults. Although the effectiveness of plasma exchange treatment in children with diarrhea-associated HUS is unknown, the mortality of these children is 3% [16], and therefore plasma exchange is sometimes used in children with severe neurologic abnormalities. Children who have renal failure but who do not have a diarrhea prodrome are described as atypical HUS. Their management is uncertain, but may include plasma exchange treatment when neurologic involvement or renal failure is severe. Children without renal failure are uncommon; they are described as TTP and managed as adults with TTP.

TTP can be caused by congenital ADAMTS13 deficiency, which may initially present either in children or adults [17]. We have not recognized a patient with congenital TTP among our 382 patients; all patients in whom we have identified with ADAMTS13 deficiency appeared to have an acquired disorder. Atypical HUS may be caused by a congenital abnormality of complement activation [18]; among the three children with atypical HUS in the Registry, we have not measured complement regulatory proteins.

For some categories of patients, we have created new rules to fit exceptional clinical situations. For patients who predictably do not respond to plasma exchange treatment, it is appropriate to use the term TMA, a histologic descriptive term common to multiple disorders of diverse etiologies that are often most prominent in the kidney [19], rather than TTP (Table II). Changing the name from TTP to TMA is a simple way to avoid consideration of plasma exchange. For example, we no longer treat patients who develop microangiopathic hemolytic anemia and thrombocytopenia following allogeneic hematopoietic stem cell transplantation with plasma exchange. Therefore we describe these patients as having transplantation-associated TMA [20]. Microangiopathic hemolytic anemia and thrombocytopenia caused by multiple diverse etiologies are also common in patients with HIV infection and advanced acquired immune deficiency syndrome (AIDS) [21]. Some of these patients may have TTP and plasma exchange treatment may be effective; but in others plasma exchange treatment may not be effective and therefore the term HIV-associated TMA may be more appropriate [22]. Some patients who have a gradual onset of dose-dependent drug toxicity from chemotherapeutic agents may fulfill diagnostic criteria for TTP but may not respond to plasma exchange treatment; they may be described by the term chemotherapy-associated TMA. Patient enrollment in the Registry is based on the request for plasma exchange treatment for TTP or HUS. Therefore, all patients were initially considered to have TTP or HUS, even though retrospectively we may have changed the name of their disorder to TMA.

TABLE III. Clinical Value of ADAMTS13 Activity Measurements

ADAMTS13 activity	Clinical value
ADAMTS13 <5%	Specific for TTP (with rare reported exceptions: severe sepsis, severe liver disease) Not sensitive to detect all patients with TTP who may relapse or may benefit from plasma exchange treatment
ADAMTS13 <10%	Sensitive to detect all patients with TTP who may relapse (with rare exceptions) Not specific for TTP; may include patients with sepsis, malignancy, and post-transplantation TMA Not sensitive to detect all patients with TTP who may benefit from plasma exchange treatment
ADAMTS13 10–50%	Includes patients with acute disorders of diverse etiologies; also women near term of normal pregnancy Some patients in this range may benefit from plasma exchange treatment
ADAMTS13 >50%	Normal Some patients with normal ADAMTS13 activity may benefit from plasma exchange treatment

Adults who have a prodrome of bloody diarrhea associated with *E. coli* O157:H7 infection may be appropriately described by the comprehensive term, TTP-HUS, since they have some demographic and clinical features similar to adults with severe ADAMTS13 deficiency, including apparent response to plasma exchange treatment, and other demographic and clinical features similar to children with typical diarrhea-associated HUS [16].

ADAMTS13 Activity

Severe ADAMTS13 deficiency has been described as a specific abnormality for TTP [6], but the level of ADAMTS13 activity that defines a ''severe'' deficiency is not established. In our experience, ADAMTS13 activity less than 5% is specific for syndromes that have the typical clinical features of TTP (Table III). Although there are reports of undetectable ADAMTS13 activity in patients with sepsis [23,24] and severe liver disease [25], this has not occurred in Registry patients. Although ADAMTS13 activity <5% may be specific for TTP, this stringent definition of severe ADAMTS deficiency excludes some patients who have typical

features of TTP including multiple relapses. If the definition of severe deficiency is expanded to include all patients with ADAMTS13 activity less than 10%, these patients are included [26]. But this expanded definition then also includes patients whose clinical course was not typical for TTP and in whom severe sepsis or disseminated malignancy was subsequently discovered to be the more likely etiology of their presenting features. Most patients with ADAMTS13 activity <10% were in the idiopathic category; some presented postpartum or with bloody diarrhea, or had an additional diagnosis of systemic lupus erythematosus (SLE). Some patients have had persistent severe ADAMTS13 deficiency with a demonstrable inhibitor after recovery but with no signs of TTP, suggesting that ADAMTS13 deficiency alone is not sufficient to cause TTP.

In the following descriptions, we use the term ADAMTS13 deficiency to indicate ADAMTS13 activity <10%. Not all patients who may benefit from plasma exchange treatment have ADAMTS13 deficiency. For example, we treat patients with quinine-associated TTP or TTP-HUS following a prodrome of bloody diarrhea with plasma exchange despite expected normal ADAMTS13 activity because they fulfill the diagnostic criteria of TTP, they are often critically ill, the etiology is not certain, and other patients with normal ADAMTS13 activity appear to benefit from plasma exchange treatment.

TABLE IV. Presenting Clinical Features of 18 Patients with TTP and ADAMTS13 Activity <5%[d]

Clinical features	Patients (number)
Presenting symptoms[a]	
Abdominal pain	6
Nausea, vomiting, diarrhea	5
Minor neurologic abnormalities[b]	5
Severe neurologic abnormalities[c]	3
Fever	4
Weakness, dyspnea	3
Chest pain	3
Hematuria	2
Laboratory abnormalities	
Thrombocytopenia	18
Microangiopathic hemolytic anemia	18
Renal function abnormalities	
Acute renal failure[d]	1
Minor renal insufficiency[e]	7
Normal renal function[f]	10
Complete pentad of clinical features[g] present	0

[a]The number of presenting symptoms exceeds 18 because some patients had more than one prominent presenting symptom.
[b]Confusion, disorientation (4 patients), ataxia (1), headache (1).
[c]Focal abnormalities (4 patients), seizure (2), aphasia (2).
[d]Increased serum creatinine ≥0.5 mg/dL on 2 consecutive days or creatinine ≥4.0 mg/dL and dialysis within 7 days of diagnosis[d].
[e]Serum creatinine ≥1.5 mg/dL within 7 days of diagnosis.
[f]Serum creatinine values all <1.5 mg/dL.
[g]Thrombocytopenia, microangiopathic hemolysis, neurologic and renal abnormalities, fever.

Diagnosis

The common presenting complaints of patients with TTP and ADMTS13 activity <5% are abdominal pain, nausea, vomiting, and/or diarrhea (Table IV). These are common symptoms seen by doctors every day, often causing the diagnosis of TTP to be often overlooked until laboratory data are obtained. Delay of diagnosis may occur because laboratory data are often not obtained for these common symptoms.

Laboratory data provide the diagnostic criteria: thrombocytopenia and microangiopathic hemolytic anemia. The third and most important diagnostic criterion, no apparent alternative etiology, requires careful clinical evaluation. Microangiopathic hemolysis is confirmed by the presence of red cell fragments on the peripheral blood smear, a negative direct antiglobulin (Coombs') test, and elevated serum levels of indirect bilirubin and LDH. These minimal diagnostic criteria are validated by the presenting features of patients with ADAMTS13 activity less than 5% (Table IV). Among 18 consecutive patients [4,10], 10 had no neurologic abnormalities, not even minor abnormalities such as headache, ataxia, and confusion. Ten had normal renal function. Fever was present in only 4 patients. The complete "classic pentad" of clinical features (anemia, thrombocytopenia, neurologic and renal abnormalities, and fever), described before the era of effective treatment [27], was not present in any of these 18 patients. Therefore, the pentad must be discarded as a description of patients with TTP.

Acute episodes of TTP may be triggered by other stressful conditions and these associated conditions often create a diagnostic dilemma. Pregnancy, especially near term or postpartum, has a clear association with acute episodes of both congenital and acquired TTP [17,28]. In pregnant or postpartum women, it may not be possible to initially distinguish TTP from severe preeclampsia or the HELLP (hemolysis, elevated liver function tests, and low platelets) syndrome [29]. Acute inflammatory disorders, such as pancreatitis, can trigger acute episodes of TTP [30]. A variety of infections has also been associated with the onset or exacerbation of acute episodes of TTP [31]. Physicians may be reluctant to consider TTP in patients with an established diagnosis of pancreatitis or an infection.

The reverse situation, considering an alternative diagnosis in a patient with an established diagnosis of TTP, also creates a diagnostic dilemma. We have seen multiple distinct disorders that have been misdiagnosed as TTP and then subsequently, unexpectedly discovered (Table I): sepsis caused by bacteria (e.g., Group A Streptococcus), viruses (e.g., Cytomegalovirus), fungi

(e.g., Aspergillus) and Rickettsiae (e.g., Rocky Mountain spotted fever) [32]. Many different types of disseminated malignancies can mimic TTP [33]. Malignant hypertension may present with all of the clinical features of TTP [34]. The diagnosis of TTP may be considered in patients who are severely ill with multiorgan failure of uncertain etiology because physicians are desperate for any effective treatment; in our experience plasma exchange has been ineffective in these patients. Continued vigilance for alternative etiologies is required even after plasma exchange treatment for TTP has begun.

Management

To accurately analyze the clinical course and response to treatments, we established quantitative and reproducible outcome definitions [4]. Response to treatment is defined as the achievement of a normal platelet count, over 150,000/μL, during plasma exchange treatment or within 1 week of stopping treatment. The clinical value of other parameters, such as LDH levels, seems less important. Exacerbation of a continuing episode is defined as recurrent thrombocytopenia following a response plus resumption of daily plasma exchange treatment after less than 30 days of no plasma exchange treatment. Remission is defined as no plasma exchange treatment for more than 30 days. Relapse, a distinct new episode of TTP, is defined as treatment for a new episode following a remission.

Plasma exchange is the only treatment for TTP supported by firm clinical evidence [10]. Our practice is to exchange one plasma volume daily until the platelet count is normal for 2 days (Table V). Decisions regarding additional treatment and how plasma exchange should be stopped when a response occurs are often related to our level of suspicion for ADAMTS13 deficiency (Table V). ADAMTS13 deficiency is suspected in patients with idiopathic TTP who do not have acute renal failure and in patients who exacerbate when daily plasma exchange stopped; ADAMTS13 deficiency is assumed in all patients with relapsed episodes. The number of plasma exchange treatments to achieve a remission is extremely variable, from less than five to more than 70 treatments over several months.

Patients who have suspected or known ADAMTS13 deficiency are also treated with glucocorticoids (Table V). Patients who have exacerbations despite glucocorticoid treatment may be treated with more intensive immunosuppressive agents, such as rituximab [35]. Patients who have neurologic abnormalities that occur despite daily plasma exchange are treated with twice-daily plasma exchange, until the patient's platelet count begins to increase and neurologic complications begin to resolve [36], in addition to intensive immunosuppressive therapy.

TABLE V. Management of Patients with TTP

Treatment modality	Clinical use
Plasma exchange	One plasma volume exchanged daily until platelet count is >150,000/μL for 2 days No difference among different plasma preparations (fresh frozen plasma, 24 hour plasma, cryosupernatant plasma) Twice-daily treatments may be beneficial in critically ill patients with new neurologic abnormalities who have failed to respond to daily treatment [36] In patients without suspected ADAMTS13 deficiency, treatments may be stopped abruptly; in patients with suspected ADAMTS13 deficiency, tapering of treatments may be necessary A 28% rate of major complications and 2.4% mortality have been attributed to plasma exchange [40]
Steroids	Prednisone, I mg/kg/day, is appropriate adjunctive treatment for patients with suspected ADAMTS13 deficiency Higher doses (e.g., methylprednisolone, 1000 mg/day for 3 days) may be beneficial in critically ill patients
Rituximab	May be beneficial in patients who fail to achieve a response or remission with plasma exchange and steroids [35]
Aspirin	Not used as routine adjunctive treatment Appropriate for routine indications (e.g., transient cerebral or cardiac ischemic events) when platelet count >30,000/μL

We do not use aspirin or other agents that inhibit platelet function as adjunctive treatment for TTP. Aspirin is appropriate for patients who have the standard indications of cardiac or neurologic ischemic symptoms and do not have severe thrombocytopenia. Bleeding symptoms are uncommon, but when severe bleeding occurs or a surgical procedure is required in a patient with severe thrombocytopenia, we do not withhold platelet transfusions. We have observed no significant relation between platelet transfusions and adverse outcomes [37].

When a remission is achieved, we gradually increase the interval for laboratory evaluation over several months and then recommend only careful routine care by the patient's primary physician. The most critical aspect of continuing care is to instruct the patient to obtain a platelet count immediately when any acute symptoms occur. We emphasize this repeatedly because any symptom – gastrointestinal, respiratory, unusual headache – may be an indication of relapse. We emphasize this directly to the patient because primary care physicians may not routinely obtain platelet counts for a minor illness.

Although the risk for relapse is high in patients with severe ADAMTS13 deficiency, there is no established role for consolidation or maintenance immunosuppressive treatment. The value of ADAMTS13 measurements during remission is not known; patients may have persistent ADAMTS13 deficiency for many years with no evidence of TTP.

Complications of Plasma Exchange Treatment

We document adverse events with each plasma exchange treatment. Among 206 consecutive patients over 9 years, 57 (28%) had major complications and 5 (2.4%) patients died, attributed to plasma exchange [38–40]. Deaths were caused by hemorrhagic or pneumothorax complications of central venous catheter insertion (3 patients) or sepsis attributed to the central venous catheter (2 patients) [40]. Two additional patients have had cardiac arrest with pulseless electrical activity: one caused by an anaphylactic reaction to plasma and the other caused by cardiac tamponade related to catheter insertion. These high risks are distinct from a recent large study of patients treated with plasma exchange that reported no deaths [41]. However that study only included patients who began plasma exchange treatment, potentially excluding complications from central venous catheter insertion [41]. Also patients with TTP may be sicker and may require more plasma exchange treatments than some other patients treated with plasma exchange.

Mortality

The continuing high-risk of death from TTP can best be appreciated by analysis of patients whose diagnosis is supported by demonstration of ADAMTS13 deficiency and who are expected to respond to plasma exchange and immunosuppressive treatments. Our experience is that the mortality rate remains high. Seven (16%) of 45 patients with ADAMTS13 activity less than 5% died during their initial episode, however death was attributed to the TTP in only three (7%) patients in whom systemic microvascular thrombosis was documented by autopsy. In three other patients, death was attributed to complications of the central venous catheter: sepsis in 2 patients and hemorrhage caused by catheter insertion in 1 patient. One patient died with multiple pulmonary emboli after she had responded to plasma exchange.

Long-Term Outcomes

Risk for relapse is typically the greatest concern of both patients and physicians after recovery. Registry data have documented that relapse is common among patients with ADAMTS13 deficiency but very rare among patients without ADAMTS13 deficiency, that most initial relapses occur within the first year, that initial relapses are rare after 4 years, and that most patients have only a single relapse (Table VI) [26]. Although risk for relapse is the most common and most apparent concern following recovery from TTP, other problems affect many more patients (Table VI). Following recovery from an acute episode, many patients do not feel that they are as capable, mentally or physically, as they were before their episode of TTP. They often describe persistent problems with memory, concentration, and endurance [42]. We have documented these abnormalities with serial measurements of health-related quality-of-life [43]. We attribute these symptoms to the residual effects of microvascular thrombosis causing minor neurocognitive abnormalities affecting attention, processing speed and memory, that also may cause slower motor function and fatigue [44].

TABLE VI. Potential Long-Term Risks Following Recovery from Thrombotic Thrombocytopenic Purpura

Outcome	Occurrence
Relapse	Apparently restricted to patients with ADAMTS13 deficiency Approximately 40% of patients with ADAMTS13 deficiency will relapse Most relapses occur within the first year; relapses after 4 years are uncommon Most patients have only one relapse
Abnormal health-related quality-of-life[a]	May affect many patients, regardless of clinical category May be related to minor abnormalities of cognitive function caused by cerebral microvascular thrombosis May persist over many years

[a]Scores by a standard evaluation are significantly less than the US population [43].

CONCLUSIONS

Evaluation of patients with suspected TTP is a challenge for expert clinicians. Plasma exchange remains the essential treatment, although the risk for major complications is high. ADAMTS13 measurements may not help the initial decision to begin plasma exchange, but documenting ADAMTS13 deficiency is important for consideration of adjunctive immunosuppressive treatment and to anticipate the risk for relapse. With appropriate treatment, mortality from TTP may be less than 10%. Physicians must appreciate that patients who have survived an episode of TTP may have persistent abnormalities of health-related quality-of-life, resulting from difficulties with memory, concentration, and endurance.

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