The thrombotic thrombocytopenic purpura and hemolytic uremic syndromes: evaluation, management, and long-term outcomes experience of the Oklahoma TTP-HUS Registry, 1989–2007

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The Oklahoma thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) Registry, an inception cohort of 382 consecutive patients with TTP–HUS, provides a complete community perspective of these syndromes. TTP, as defined by thrombocytopenia and microangiopathic hemolytic anemia without an alternative etiology, is the appropriate term for all adults. These limited diagnostic criteria are supported by the presenting features of patients with ADAMTS13 deficiency, in whom both neurologic and renal abnormalities are uncommon. HUS is the appropriate term for children who fulfill these diagnostic criteria and who also have renal failure. These definitions are consistent with current management: plasma exchange is the essential treatment for most adults; supportive care is sufficient for children with HUS. Plasma exchange treatment has decreased the mortality of TTP from 90 to 10%. Patients with acquired autoimmune ADAMTS13 deficiency may also require immunosuppressive treatment to achieve a durable remission. Recovery has revealed previously unrecognized long-term risks. Recurrent acute episodes occur in approximately 40% of patients with acquired ADAMTS13 deficiency; most relapses occur within the first year and most patients have only one relapse. Adults with TTP of any etiology have a high risk for persistent minor cognitive abnormalities.

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Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) describe disorders of multiple etiologies. The experience of the Oklahoma TTP-HUS Registry provides a basis for evaluation and management and for anticipating long-term outcomes.

DIAGNOSTIC CRITERIA FOR TTP AND HUS

In the era before effective treatment, TTP was defined by a pentad of clinical features, namely thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, renal failure, and fever.[1] The availability of effective treatment with plasma exchange required urgency for diagnosis and decreased stringency of diagnostic criteria. The current diagnostic criteria are only thrombocytopenia and microangiopathic hemolytic anemia, without an apparent alternative etiology.[2,3] The validity of these limited criteria is supported by the presenting features of patients whose diagnosis of TTP was supported by the presence of severe ADAMTS13 deficiency: neurologic and renal abnormalities were uncommon, fever was rare, and no patients had the complete pentad of clinical features (Table 1).[4] The availability of effective treatment and the limited diagnostic criteria have resulted in an 8- to 10-fold increase in patients treated with plasma exchange for TTP.[5,6]

As the diagnosis of TTP requires consideration of plasma exchange treatment, and because almost all adults who fulfill the diagnostic criteria for TTP may benefit from plasma exchange, we use the diagnostic term TTP for almost all adults. We restrict the term HUS to children who fulfill the diagnostic criteria of thrombocytopenia and microangiopathic hemolytic anemia and who also have renal failure. Overall 90% of children with HUS have a diarrhea prodrome, caused mostly by *Escherichia coli* O157:H7;[7] their mortality is 3% with supportive care;[8] therefore, plasma exchange is rarely requested. As children with HUS are not treated with plasma exchange, the use of the term HUS in adults may imply that plasma exchange is unnecessary. Therefore, we avoid the term HUS for adults, even adults with acute renal failure.

Table 1 | Presenting clinical features of the initial 18 patients in the Oklahoma TTP-HUS Registry whose diagnosis was supported by ADAMTS13 activity <5%[4]

Clinical features	Patients (*n*)
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

TTP-HUS, thrombotic thrombocytopenic purpura-hemolytic uremic syndrome.
[a]The number of presenting symptoms exceeds 18 because some patients had more than one prominent presenting symptom. Thrombocytopenia and microangiopathic hemolytic anemia were required criteria for diagnosis of TTP and inclusion in the Registry.
[b]Confusion, disorientation (4 patients), ataxia (1), and headache (1).
[c]Focal abnormalities (4 patients), seizure (2), and aphasia (2).
[d]Increased serum creatinine $\geqslant$44 μmol/l on 2 consecutive days or creatinine $\geqslant$354 μmol/l and dialysis within 7 days of diagnosis.[4]
[e]Serum creatinine $\geqslant$133 μmol/l within 7 days of diagnosis.
[f]Serum creatinine values all <133 μmol/l.
[g]Thrombocytopenia, microangiopathic hemolysis, neurologic and renal abnormalities, and fever.

DISORDERS THAT CAN MIMIC THE CLINICAL PRESENTATION OF TTP

As the diagnostic criteria for TTP are not specific, multiple systemic disorders can mimic TTP, resulting in mistaken diagnosis. These include disseminated malignancies,[9,10] systemic infections,[11–14] malignant hypertension,[15,16] systemic lupus erythematosus,[17] and other renal disorders.[16] Therefore, physicians must maintain continued vigilance for alternative disorders even after a diagnosis of TTP is apparently established and plasma exchange treatment has begun.

DIAGNOSTIC AND PROGNOSTIC VALUE OF ADAMTS13 MEASUREMENTS

ADAMTS13 measurements may not assist initial diagnosis and management decisions but are important for prognosis. Although most patients with severe ADAMTS13 deficiency have no renal insufficiency, causing initial reports to suggest that ADAMTS13 activity measurements may distinguish TTP from HUS,[18] some patients with severe ADAMTS13 deficiency have acute renal failure (Table 1). ADAMTS13 activity <5% appears to be specific for TTP but does not identify all patients who may relapse; ADAMTS13 activity <10% essentially identifies all patients who are at risk for relapse but is not specific; patients with sepsis[19,20] and liver cirrhosis[21] may also have ADAMTS13 activity <10%.

DEFINITIONS OF OUTCOMES

Reproducible definitions are required to accurately analyze the clinical outcomes of patients with TTP.[4] Response is defined as the achievement of a normal platelet count; other parameters seem less important. Exacerbation of a continuing episode is defined as the recurrence of TTP within 30 days of stopping plasma exchange treatment. Remission is defined as a normal platelet count for 30 days after stopping plasma exchange treatment. Relapse, a distinct new episode of TTP, is defined as recurrent TTP occurring more than 30 days after stopping plasma exchange. The 30-day interval is important because patients with ADAMTS13 deficiency commonly have exacerbations of continuing disease when plasma exchange treatment is stopped.

PLASMA EXCHANGE TREATMENT

Plasma exchange is the essential treatment for all patients who are diagnosed with TTP, with or without renal failure,[2,22] but the number of plasma exchange treatments to achieve a remission is extremely variable. Among our patients with severe ADAMTS13 deficiency, the number of plasma exchange treatments required to achieve a remission ranged from 3 to 89.[4]

A hypothesis for the efficacy of plasma exchange is that ADAMTS13 deficiency is corrected by plasma infusion and that ADAMTS13 inhibitor is removed by apheresis.[23] However, the majority of adults diagnosed with TTP do not have severe ADAMTS13 deficiency, and many also appear to respond to plasma exchange, such as patients who present with bloody diarrhea or who have quinine-induced TTP.[4,8,24] The mechanism of possible plasma exchange efficacy in these patients is unknown.

COMPLICATIONS OF PLASMA EXCHANGE TREATMENT

The decision to initiate plasma exchange treatment must balance potential complications with confidence in the diagnosis of TTP. Among 206 consecutive patients over 9 years in the Oklahoma Registry, 57 (28%) had major complications and 5 (2.4%) deaths were attributed to plasma exchange.[25–27] Deaths were caused by hemorrhagic or pneumothorax complications of central venous catheter insertion (two patients) or sepsis attributed to the central venous catheter (three patients). Two additional patients had cardiac arrests with pulseless electrical activity: one caused by an anaphylactic reaction to plasma and the other caused by cardiac tamponade related to catheter insertion.

ADJUNCTIVE TREATMENT

Treatment with immunosuppressive agents is reserved for patients with suspected autoimmune ADAMTS13 deficiency. Corticosteroids are the initial immunosuppressive agents; other agents, such as rituximab[28] and cyclosporine,[29] are used for patients with a more critical course. Aspirin is not used as adjunctive treatment but is appropriate for patients who have a standard cardiac or neurologic indication and do not have severe thrombocytopenia.

MORTALITY

In spite of optimal management, mortality among patients with TTP remains approximately 15%. However, half of these deaths may be attributed to complications of plasma exchange treatment or hospitalization, such as sepsis, hemorrhage, and thrombosis.

MANAGEMENT OF PATIENTS WHO HAVE ACHIEVED A REMISSION

Among patients with severe ADAMTS13 deficiency, the risk for relapse is approximately 40%. The value of maintenance immunosuppressive treatment or measurement of ADAMTS13 activity during remission is unknown. Patients may have severe ADAMTS13 deficiency for many years with no evidence of TTP. The critical element of continuing care is to insist that patients obtain a platelet count immediately when any acute symptoms occur, as any symptom may indicate recurrent TTP.

LONG-TERM OUTCOMES

Although relapse may be the greatest concern, other problems affect many more patients. After recovery, patients have significantly abnormal health-related quality of life;[30] neurocognitive studies have documented deficits of attention, processing speed and memory, and also fatigue.[31]

DISCLOSURE

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