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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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

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Presenting symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6</td>
</tr>
<tr>
<td>Nausea, vomiting, diarrhea</td>
<td>5</td>
</tr>
<tr>
<td>Minor neurologic abnormalitiesa</td>
<td>5</td>
</tr>
<tr>
<td>Severe neurologic abnormalitiesc</td>
<td>3</td>
</tr>
<tr>
<td>Fever</td>
<td>4</td>
</tr>
<tr>
<td>Weakness, dyspnea</td>
<td>3</td>
</tr>
<tr>
<td>Chest pain</td>
<td>2</td>
</tr>
<tr>
<td>Hematuria</td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory abnormalities</strong></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>18</td>
</tr>
<tr>
<td>Microangiopathic hemolytic anemia</td>
<td>18</td>
</tr>
<tr>
<td>Renal function abnormalities</td>
<td></td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>1</td>
</tr>
<tr>
<td>Minor renal insufficiency</td>
<td>7</td>
</tr>
<tr>
<td>Normal renal function</td>
<td>10</td>
</tr>
<tr>
<td><strong>Complete pentad of clinical featuresb</strong></td>
<td>0</td>
</tr>
</tbody>
</table>

TTP-HUS, thrombotic thrombocytopenic purpura-hemolytic uremic syndrome.

aThe 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.

bConfusion, disorientation (4 patients), ataxia (1), and headache (1).

The mechanism of possible plasma exchange efficacy in these patients is unknown.

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 rituximab28 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; cognitive studies have documented deficits of attention, processing speed and memory, and also fatigue.

DISCLOSURE
The author has declared no financial interests.

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REFERENCES