

# The thrombotic thrombocytopenic purpura and hemolytic uremic syndromes: overview of pathogenesis (Experience of The Oklahoma TTP-HUS Registry, 1989–2007)

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The Oklahoma TTP (thrombotic thrombocytopenic purpura)—HUS (hemolytic uremic syndrome) Registry, an inception cohort of 382 consecutive patients with TTP-HUS, provides a complete community perspective of these syndromes. TTP is the diagnostic term used for all adults, with or without neurologic or renal abnormalities; it is typically an acquired disorder; it may rarely result from congenital ADAMTS13 deficiency. HUS is the term used for children who have renal failure, most often caused by *Escherichia coli* O157:H7 infection; it may rarely result from congenital abnormalities of complement regulation. Clinical categories related to associated conditions and potential etiologies provide a structure for describing pathogenesis of the acquired syndromes. (1) Following allogeneic hematopoietic stem cell transplantation; a disorder primarily affecting kidneys described as transplantation-associated thrombotic microangiopathy. (2) Pregnancy-associated; pregnancy is a prominent risk factor for the development of TTP. (3) Drug-associated; acute, immune-mediated systemic syndromes and also dose-dependent renal toxicity. (4) Bloody diarrhea prodrome, suggesting an enteric infectious etiology. (5) Presence of an additional autoimmune disorder. (6) Idiopathic. A severe deficiency of ADAMTS13 activity contributes to the pathogenesis of many idiopathic patients and also some patients who present during pregnancy, with bloody diarrhea, or who have additional autoimmune disorders.

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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 definitions of these syndromes and for clinical categories that are relevant for understanding the pathogenesis as well as for guiding evaluation and management.

## THE OKLAHOMA TTP-HUS REGISTRY

The Oklahoma TTP-HUS Registry is an inception cohort of all 382 consecutive patients from 58 of Oklahoma's 77 counties for whom plasma exchange treatment was requested for TTP or HUS from 1989 through 2007.<sup>1–3</sup> ADAMTS13 activity has been analyzed in 235 (93%) of 254 patients since 1995 at the University of Berne, Switzerland, by Drs Bernhard Lämmle and Johanna Kremer Hovinga. Patients are described by clinical categories, related to their associated conditions and clinically apparent etiologies (Table 1) and also by the presence of severe ADAMTS13 deficiency.

## DEFINITIONS OF TTP AND HUS

TTP is defined by (1) thrombocytopenia, (2) microangiopathic hemolytic anemia, and (3) no alternative explanations.<sup>4,5</sup> TTP is an appropriate diagnostic term for adults who fulfill these diagnostic criteria, whether or not neurologic or renal abnormalities are present. TTP is an appropriate diagnostic term because plasma exchange is essential treatment for almost all adults, and the term TTP requires consideration of plasma exchange. HUS is not an appropriate diagnostic term for adults because it may imply that plasma exchange treatment is unnecessary. Exceptions to this nomenclature rule are made for patients who predictably do not respond to plasma exchange, such as following allogeneic hematopoietic stem cell transplantation. To avoid consideration of plasma exchange treatment, these patients are described by the pathologic term, thrombotic microangiopathy,<sup>6</sup> a term that also describes conditions such as malignant hypertension and systemic sclerosis.<sup>7</sup>

**Table 1 | Clinical categories of the 382 patients enrolled in the Oklahoma TTP-HUS Registry, 1989-2007**

Category	Patients
<i>Clinically diagnosed patients: diagnosed and enrolled at the time of their initial episode</i>	
Allogeneic stem cell transplant	23
Pregnant/postpartum	26
Drug-associated	47
Acute (immune-mediated)	27
Chronic (dose-dependent toxicity)	20
Bloody diarrhea prodrome	27
Additional or alternative disorder	99
Idiopathic	140
Total	362
Clinically diagnosed patients: enrolled at the time of their second or later episode	8
Patients diagnosed by renal biopsy: enrolled at the time of their initial episode	12
Total number of patients	382

HUS, hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura. Patients who were clinically diagnosed at the time of their initial episode were assigned in a hierarchical, sequential order to one of the six clinical categories related to associated conditions and potential etiologies that were clinically apparent during their initial episode. Patients enrolled at the time of their second or later episode would have all been in the idiopathic category. Patients diagnosed by renal biopsy are distinct because they may not fulfill the clinical diagnostic criteria; for example, some were not thrombocytopenic; some did not have evidence for microangiopathic hemolytic anemia.

TTP is almost always an acquired syndrome. The etiology may be autoimmune, associated with a severe deficiency of ADAMTS13, but there are also multiple other etiologies. TTP may rarely be caused by a congenital deficiency of ADAMTS13 activity. Congenital TTP often presents in infancy but may not present until a triggering event, such as pregnancy, occurs.

HUS is the accepted diagnostic term for children who fulfill the diagnostic criteria of thrombocytopenia and microangiopathic hemolytic anemia and who also have renal failure. Children with HUS are divided into two categories: (1) children who have diarrhea-associated HUS, an acquired disorder caused by a Vero toxin-producing enteric infection, typically *Escherichia coli* O157:H7;<sup>8</sup> (2) children described as diarrhea-negative HUS, who are heterogeneous. Some children without diarrhea also have infectious etiology, such as *Streptococcus pneumoniae*,<sup>9</sup> whereas others may have congenital abnormalities of complement regulation.<sup>10</sup> It is only rarely that children who fulfill the diagnostic criteria of thrombocytopenia and microangiopathic hemolytic anemia do not have renal failure; they are appropriately described as TTP. As plasma exchange is not the standard treatment for children with HUS, children are underrepresented in the Oklahoma Registry.

## DEMOGRAPHICS

The age-sex-race standardized annual incidence rates were 11.3 per 10<sup>6</sup> for all Registry patients and 1.7 per 10<sup>6</sup> for

patients with ADAMTS13 activity <5%.<sup>11</sup> Among patients with ADAMTS13 activity <5%, the median age was 40 years and there were significant sex and race disparities. The age-sex-race standardized incidence rate ratio for blacks to non-blacks was 9.3, and that for women to men was 2.7,<sup>11</sup> similar to the demographics of systemic lupus erythematosus.<sup>12</sup>

## PATHOGENESIS: ADAMTS13 DEFICIENCY

Among Registry patients, about 15% of all patients and about half of the patients with idiopathic TTP have severe ADAMTS13 deficiency (currently defined as <10% activity).<sup>1</sup> ADAMTS13 deficiency alone may not be sufficient to cause TTP. Some patients have persistent severe ADAMTS13 deficiency, either congenital or acquired with a demonstrable autoantibody inhibitor, but have no clinical signs of TTP. Additional conditions, such as infections,<sup>13</sup> acute inflammatory conditions such as pancreatitis,<sup>14</sup> or pregnancy,<sup>15</sup> may be required to trigger acute episodes of TTP in patients with ADAMTS13 deficiency.

## PATHOGENESIS: CLINICAL CATEGORIES

### Hematopoietic stem cell transplantation

The syndrome following allogeneic stem cell transplantation was initially described as TTP and therefore was often treated with plasma exchange (Table 1), but this disorder is limited to renal thrombotic microangiopathy,<sup>16</sup> does not respond to plasma exchange,<sup>17</sup> and is now described as transplantation-associated thrombotic microangiopathy.<sup>16</sup>

### Pregnancy

Pregnancy-related syndromes (severe preeclampsia, HELLP syndrome) may be indistinguishable from TTP.<sup>18</sup> Pregnancy is also an established risk for triggering acute episodes of TTP, most often in the third trimester or postpartum.<sup>15</sup> Although this causes concern about the risk of future pregnancies, recurrent TTP with a subsequent pregnancy is uncommon among women in the Oklahoma Registry: TTP was diagnosed during a subsequent pregnancy in five (14%) women among 36 pregnancies.<sup>19</sup>

### Drug association

Drugs seem to cause TTP by at least two mechanisms: (1) acute onset, systemic, presumably immune-mediated. Quinine was the etiology in 23 (88%) of 27 patients. Racial and sex disparities are remarkable among patients with quinine-induced TTP: over 90% were women, similar to all other categories of TTP; over 90% were white,<sup>20</sup> opposite to the racial disparity of patients with severe ADAMTS13 deficiency.<sup>11</sup> (2) Gradual onset, presumably dose-dependent toxicity principally affecting the kidney. Mitomycin accounted for 11 (55%) of 20 patients. Some drugs causing dose-dependent toxicity may be related to inhibition of vascular endothelial growth factor.<sup>21</sup>

### Bloody diarrhea prodrome

Although a prodrome of bloody diarrhea suggests the etiology of *E. coli* O157:H7, patients with severe ADAMTS13

deficiency may also present with bloody diarrhea caused by ischemic colitis. Adults with a bloody diarrhea prodrome have some features similar to adults with severe ADAMTS13 deficiency and different from children with diarrhea-associated HUS (predominantly women, frequent severe neurologic abnormalities, high mortality); other features are similar to children with diarrhea-associated HUS and different from adults with severe ADAMTS13 deficiency (predominantly white race, frequent renal failure, no relapses).<sup>22</sup>

#### Additional disorders

Other autoimmune disorders may occur in patients with TTP, but it may also be difficult to distinguish patients with severe flares of systemic lupus erythematosus from patients with TTP. Among patients with severe ADAMTS13 deficiency, the frequency of rheumatic disease autoantibodies is high, suggesting a potential risk for developing additional autoimmune disorders.<sup>23</sup>

#### Idiopathic

Patients not assigned to any of the previous five categories are described as idiopathic. Approximately half of the patients with idiopathic TTP have ADAMTS13 deficiency. The etiology of TTP in patients who do not have severe ADAMTS13 deficiency is unknown.

#### DISCLOSURE

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