CME/SAM

Platelet Count and Prothrombin Time Help Distinguish Thrombotic Thrombocytopenic Purpura–Hemolytic Uremic Syndrome From Disseminated Intravascular Coagulation in Adults

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Key Words: Thrombotic thrombocytopenic purpura; Hemolytic uremic syndrome; Disseminated intravascular coagulation; Prothrombin time; Thrombocytopenia

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Upon completion of this activity you will be able to:
- describe how the diagnosis of thrombotic thrombocytopenic purpura (TTP) is complicated by its similarities with other conditions such as disseminated intravascular coagulation.
- describe the current understanding of the pathophysiology of TTP.
- discuss the standard therapy for TTP and the risk of missing the diagnosis.

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Questions appear on p 512. Exam is located at www.ascp.org/ajcpcme.

Abstract

*Thrombotic thrombocytopenic purpura–hemolytic uremic syndrome (TTP-HUS) and disseminated intravascular coagulation (DIC) may have identical manifestations in adults. Because TTP-HUS is 90% fatal without plasma exchange, prompt diagnosis is essential. To test the hypothesis that routine laboratory assays can discriminate between the 2 entities, we retrospectively identified adult patients with TTP-HUS and matched each with 2 patients with DIC. Although the platelet count, prothrombin time (PT), and partial thromboplastin time were different (*P < .05*) between the 2 patient groups, after regression analysis, only PT and profound thrombocytopenia remained associated with TTP-HUS (*P = .001 *and* P = .003, respectively). A platelet count of less than 20 × 10^3/μL (20 × 10^9/L) and a PT within 5 seconds of the upper limit of the reference interval had a specificity of 92% for TTP-HUS. Our data confirm that readily available laboratory assays in the proper clinical scenario can increase the likelihood of TTP-HUS over DIC.*

Thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and disseminated intravascular coagulation (DIC) are life-threatening microangiopathic hemolytic anemias (MAHAs) with overlapping clinical and laboratory features. TTP, first described by Moschcowitz[1] in 1924, is characterized by the classic pentad of thrombocytopenia, hemolytic anemia, fever, renal dysfunction, and fluctuating neurologic status. In reality, only a minority of patients with TTP have all 5 signs. Therefore, clinical criteria for TTP have been limited to thrombocytopenia and hemolytic anemia without an alternative explanation. The prompt recognition of TTP is essential because the disease is 90% fatal without therapeutic plasma exchange (TPE).[2]

However, thrombocytopenia and hemolytic anemia are seen in many different conditions. HUS in adults, for example, is indistinguishable from TTP, and the current tendency is to use the term TTP-HUS and treat with TPE.[3-5] Other conditions are also in the differential diagnosis of thrombocytopenia and hemolytic anemia and must be suspected and, if possible, excluded before starting TPE. Markedly elevated blood pressure in malignant hypertension and current pregnancy suggesting HELLP syndrome (*h*emolytic anemia, *e*levated *l*iver enzymes, and *l*ow *p*latelets) are clinical factors that greatly facilitate the diagnosis of those specific types of MAHA. Acute DIC is, perhaps, the most difficult to distinguish from TTP-HUS because it may manifest with the complete pentad of signs in acutely ill patients.

Although there is no "gold standard" test for TTP-HUS or DIC, clinical suspicion coupled with laboratory abnormalities is the standard of care. In the last 10 years since the

discovery of the von Willebrand factor–cleaving protease (ADAMTS13), it remains debatable whether ADAMTS13 deficiency defines TTP. Although severely decreased enzyme activity (<5%) is considered specific for TTP and is seen in most patients with TTP, ADAMTS13 measurement is not considered sensitive enough to identify every patient that would benefit from TPE.[6-8] In addition, the ADAMTS13 assay is mainly available at reference laboratories, results take several days, and TPE cannot be postponed in these critically ill patients.[9] Therefore, while ADAMTS13 is a useful test for patients suspected of having TTP-HUS, it is not available during the initial evaluation of the patient.

Although systemic platelet thrombi are the hallmark of TTP, and fibrin deposition in the kidneys characterizes HUS, when considered together in clinical practice, it is conceivable that evidence of activation of secondary hemostasis be present at the time of diagnosis.[10-15] The aim of this study was to investigate the possibility that routine laboratory tests such as the CBC, prothrombin time (PT), partial thromboplastin time (PTT), D-dimer, fibrinogen, and lactate dehydrogenase (LDH) could discern between TTP-HUS and DIC. The choice of these tests is based on their wide availability, including in physician office laboratories, at the patient's initial evaluation. In this retrospective case-controlled study, we searched for test results or combinations of results that could increase the likelihood of TTP-HUS over DIC in adult patients in order to guide the decision to refer them for emergency TPE.

Materials and Methods

Data Collection

We retrospectively identified patients with TTP-HUS from the records of the Apheresis Service, University of Alabama at Birmingham (UAB) Hospital, treated from November 2001 to January 2005. Patients were diagnosed with TTP-HUS if they had thrombocytopenia (platelet count, $<150 \times 10^3/\mu L$ [$150 \times 10^9/L$]) and anemia with signs of hemolysis, including an elevated LDH level, decreased haptoglobin concentration, and/or schistocytes on a peripheral smear with no other likely explanation of the findings. We included in the study every patient who had the following tests before TPE: CBC, PT, PTT, D-dimer, and creatinine, as well as a documented clinical course consistent with TTP-HUS. In addition, if the patient had fibrinogen and/or LDH testing performed before TPE, the result(s) was recorded. For each patient with TTP-HUS identified, we matched 2 control subjects of similar age, sex, and race from a preexisting database of patients with DIC from the UAB medical intensive care unit. Inclusion criteria for the control subjects were thrombocytopenia (platelet count, $<150 \times 10^3/\mu L$ [$150 \times 10^9/L$]) and a clinical diagnosis of DIC upon discharge from the hospital, with or without documented infection. In addition, the control group had to have the same admission laboratory tests as listed for patients with TTP-HUS. All clinical and laboratory data were obtained from the computerized medical records after the study was approved by the institutional review board of the university.

Definition of Terms

Renal dysfunction was defined as a serum creatinine level of more than 1.3 mg/dL (115 μmol/L). Neurologic abnormalities were defined as any symptoms such as headache, mental status changes, acute confusion, coma, stroke, seizure, or focal deficits such as diplopia or aphasia.

Laboratory Assays

All laboratory tests were ordered during routine medical care, processed according to good laboratory practices, and performed at the UAB Hospital as soon as ordered by the patient's physician. No delay or freezing of samples for later testing occurred. CBCs were performed in the Coulter LH 700 (Beckman Coulter, Fullerton, CA) analyzer and the coagulation assays in the STA-R Evolution (Diagnostica Stago, Parsippany, NJ). D-dimer was measured quantitatively in plasma using the LIATest method (Diagnostica Stago). Creatinine and LDH were measured in the LX-20 (Beckman Coulter). Some patients with TTP-HUS had had pre-TPE plasma samples sent for quantitative ADAMTS13 activity and inhibitor by the collagen-binding assay at the Blood Center of Wisconsin, Milwaukee.[16] The reference ranges for ADAMTS13 activity and inhibitor are 67% to 177% and 0.4 U or less, respectively.

Statistical Analysis

Means for each assay in the TTP-HUS and DIC patient groups were compared using an independent sample *t* test. A backward stepwise regression model was performed to identify which test(s) could best differentiate TTP-HUS from DIC. All statistical analyses were done using SPSS software (SPSS, Chicago, IL).

Results

Patient Characteristics

We studied 27 adults with TTP-HUS and 51 control subjects with DIC. Three patients originally listed as having DIC had an alternative diagnosis on chart review and were excluded. Of the patients with TTP-HUS, 19 had idiopathic disease, 3 patients were postpartum, 2 patients had systemic lupus erythematosus, 1 patient was taking clopidogrel, 1 had a history of breast cancer, and 1 had pancreatic cancer and had been treated with gemcitabine. **Table 1** compares

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the demographics and clinical characteristics of the patients and the prevalence of the classic TTP-HUS pentad in both groups.

The number of TPEs per patient with TTP-HUS ranged from 4 to 41 procedures, with an average of 15. Of 12 patients who had ADAMTS13 activity and inhibitor measured, 9 had a severe deficiency (<5%) due to an inhibitor, and 3 patients had results between 49% and 60%. All 9 patients with undetectable ADAMTS13 activity had normal or slightly abnormal creatinine levels (range, 0.9-1.7 mg/dL [80-150 μmol/L]; mean, 1.3 mg/dL [115 μmol/L]). Three patients without ADAMTS13 deficiency had acute renal failure (creatinine range, 6.3-11.2 mg/dL [557-990 μmol/L]) and required dialysis.

Nineteen patients responded to TPE as defined by normalization of the platelet count and creatinine level without signs of hemolysis. Of the 8 patients who did not respond to TPE, 2 had advanced cancer, and 2 had systemic lupus erythematosus, both conditions known for their association with MAHA. In addition, their mean initial platelet count was significantly higher (P = .035) than the mean platelet count of the patients who responded to TPE, ie, $54 \times 10^3/\mu L$ ($54 \times 10^9/L$; nonresponders) and $24 \times 10^3/\mu L$, ($24 \times 10^9/L$; responders). Of the 8 patients, 5 died during hospitalization. Causes of death included respiratory failure (2 patients), pericarditis, pancreatic cancer, and multiorgan failure (1 patient each). Of the 3 survivors considered nonresponders, end-stage renal disease developed in 2, and they became dialysis-dependent despite improvement in the thrombocytopenia and hemolysis. One patient was lost to follow-up. Three patients had had a previous episode of TTP-HUS, and 1 patient had a relapse after the episode included in this study.

Among the patients with a clinical diagnosis of DIC, there were 9 with malignancies (acute myeloid leukemia and various solid tumors), 3 had HIV infection, 2 had end-stage liver disease, 1 had hemophilia, and 1 had scleroderma. In 16 patients, the diagnosis was sepsis, with or without an identified source of infection. In 12 patients there was a respiratory tract infection, and 5 patients had urinary tract infection, with or without bacteremia.

Table 1
Demographic and Presenting Characteristics of Study Cases*

Characteristic	TTP-HUS (n = 27)	DIC (n = 51)
Mean ± SD age (y)	44 ± 18	46 ± 15
F/M	19 (70)/8 (30)	35 (69)/16 (31)
African American/Caucasian/ Hispanic	13 (48)/13 (48)/1 (4)	29 (57)/22 (43)/0
Thrombocytopenia	27 (100)	51 (100)
Anemia	27 (100)	46 (90)
Fever	10 (37)	19 (37)
Renal dysfunction	19 (70)	24 (47)†
Neurologic symptoms	18 (67)	16 (31)

DIC, disseminated intravascular coagulation; HUS, hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura.
* Data are given as number (percentage) unless otherwise indicated.
† 6 of 24 patients with DIC with renal dysfunction had a history of renal insufficiency.

Laboratory Parameters

Table 2 shows the results of the univariate analysis for the laboratory parameters studied. Platelet count, PT, international normalized ratio, and PTT were statistically different (P < .05) between the 2 groups. However, after multivariate regression analysis, only PT and the degree of thrombocytopenia were statistically associated with TTP-HUS (P = .001 and P = .003, respectively) **Figure 1**. Indeed, patients with TTP-HUS were more likely to have severe thrombocytopenia and fewer abnormal coagulation studies than the DIC group: 16 (59%) and 20 (74%) of 27 patients with TTP-HUS had platelet counts less than $20 \times 10^3/\mu L$ ($20 \times 10^9/L$) and $50 \times 10^3/\mu L$ ($50 \times 10^9/L$), respectively, compared with 7 (14%) and 19 (37%) of patients with DIC (Figure 1).

Table 2
Univariate Analysis of the Relationship Between Admission Laboratory Values in Patient Groups*

Parameter	TTP-HUS (n = 27)	DIC (n = 51)	P	Reference Range
Hemoglobin, g/dL (g/L)	9.0 ± 1.8 (90 ± 18)	9.3 ± 2.0 (93 ± 20)	.440	12-14 (12-140)
Platelet count, × $10^3/\mu L$ (× $10^9/L$)	32.9 ± 32.3 (32.9 ± 32.3)	64.8 ± 36.9 (64.8 ± 36.9)	<.001	150-400 (150-400)
D-dimer, μg/mL (nmol/L)	4.425 ± 4.605 (24.23 ± 25.22)	6.254 ± 6.290 (34.25 ± 34.44)	.187	0.120-0.240 (0.66-1.31)
PT, s	15.5 ± 2.5	22.2 ± 6.2	<.001	12-14
INR	1.2 ± 0.3	2.0 ± 0.7	<.001	0.9-1.1
PTT, s	34.1 ± 15.8	48.5 ± 27.6	.015	25-35
Fibrinogen, mg/dL (g/L)†	386 ± 128 (3.9 ± 1.3)	432 ± 274 (4.3 ± 2.7)	.329	200-498 (2.0-5.0)
LDH, U/L (μkat/L)‡	1,447 ± 833 (24.2 ± 13.9)	1,654 ± 1,823 (27.6 ± 30.4)	.657	120-240 (2.0 ± 4.0)

DIC, disseminated intravascular coagulation; HUS, hemolytic uremic syndrome; INR, international normalized ratio; LDH, lactate dehydrogenase; PT, prothrombin time; PTT, partial thromboplastin time; TTP, thrombotic thrombocytopenic purpura.
* Data are given as mean ± SD.
† The fibrinogen level was measured in 46 of 51 patients with DIC.
‡ The LDH level was measured in 18 of 51 patients with DIC.

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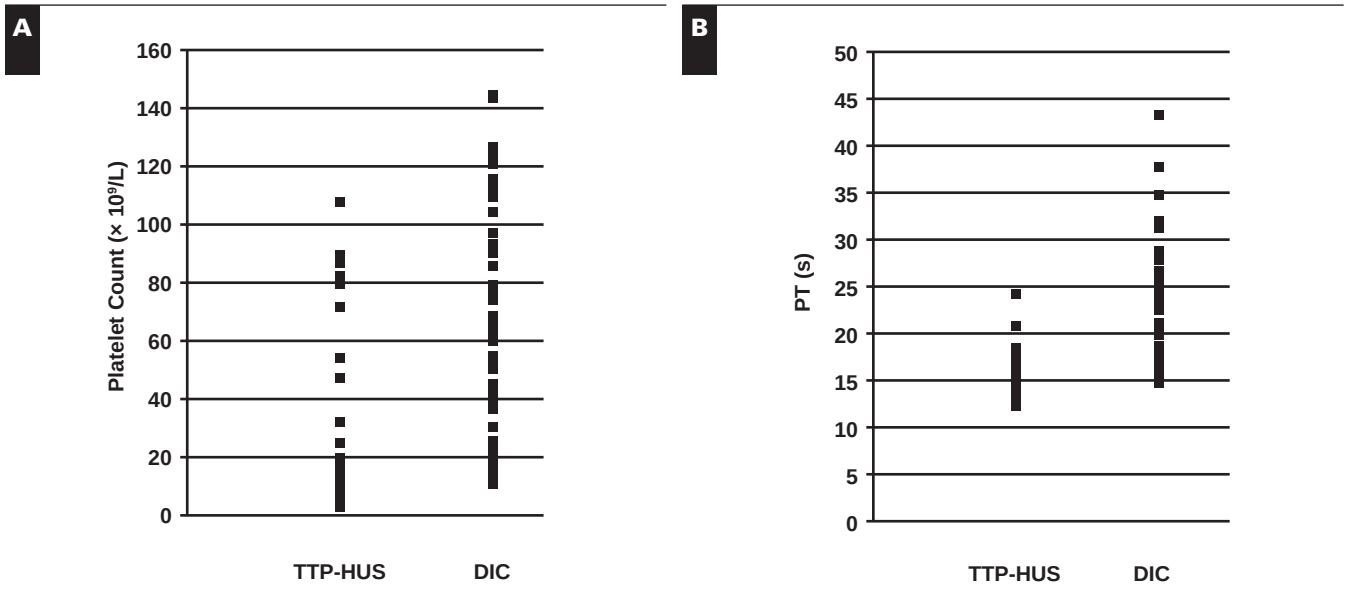

Figure 1 Comparison of platelet count (**A**) and prothrombin time (PT) (**B**) in the thrombotic thrombocytopenic purpura–hemolytic uremic syndrome (TTP-HUS) and disseminated intravascular coagulation (DIC) groups. Each point represents 1 patient at admission. Platelet counts are shown in Système International units; to convert to conventional units (× 10^3/μL), divide by 1.0. PT reference range, 12-14 s.

A platelet count less than 20 × 10^3/μL (20 × 10^9/L) was 59% sensitive and 86% specific for TTP-HUS **Table 3**. Most patients (25/27 [93%]) with TTP-HUS and fewer than half (22/51 [43%]) of patients with DIC had normal PT or results within 5 seconds of the upper limit of the reference range. Thus, the sensitivity of a mildly prolonged PT for TTP-HUS was 93% with a specificity of 57%. The combination of a platelet count less than 20 × 10^3/μL (20 × 10^9/L) and PT less than 5 seconds above the upper limit of normal was very specific for TTP-HUS (92%), although it was only 52% sensitive (Table 3). Analysis of the data without the 8 TTP-HUS nonresponders and their matched DIC control subjects increased the sensitivity and specificity of a platelet count less than 20 × 10^3/μL (20 × 10^9/L) to 74% and 89% for TTP-HUS, while the sensitivity and specificity of a mildly prolonged PT (within 5 seconds of the upper limit of normal) for TTP-HUS changed to 89% and 64%, respectively. Furthermore, the combination of both parameters was more sensitive and specific for TTP-HUS (63% and 94%, respectively). Although there was a trend for higher D-dimer concentrations in patients with DIC, D-dimer, hemoglobin, fibrinogen, and LDH values did not discriminate between the 2 groups.

Discussion

In this retrospective case-controlled study, we tested the hypothesis that readily available laboratory assays could help discriminate between TTP-HUS and DIC in adults at admission to a health care facility. We found that profound thrombocytopenia and mildly prolonged PT were the only results significantly associated with TTP-HUS. Although test results must not be used in isolation, they can reinforce the decision to quickly refer patients with TTP-HUS for TPE. As

Table 3
The Usefulness of the Platelet Count and PT for the Diagnosis of TTP-HUS

Parameter	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Platelet count <20 × 10^3/μL (20 × 10^9/L)	59	86	70	80
PT <5 s longer than ULN	93	57	53	94
Platelet count <20 × 10^3/μL (20 × 10^9/L) and PT <5 s longer than ULN	52	92	78	78

HUS, hemolytic uremic syndrome; NPV, negative predictive value; PPV, positive predictive value; PT, prothrombin time; TTP, thrombotic thrombocytopenic purpura; ULN, upper limit of normal.

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expected, patients in both disease categories had increased fibrinogen levels, consistent with an acute phase response, despite elevation in D-dimer levels, a sensitive marker of fibrin cross-linking and fibrinolysis.

In a recently published report, the 99% confidence interval for admission platelet count for 38 patients with TTP with documented ADAMTS13 deficiency due to an inhibitor was 13 to 22 × 10^3/μL (13-22 × 10^9/L).[17] These findings corroborate our suggestion that profound thrombocytopenia should significantly increase the likelihood of TTP. Because in the present report we also included patients with the clinical characteristics of HUS and we did not have ADAMTS13 activity results for most patients with TTP-HUS, the range of platelet counts in our study was wider.

Jaffe and colleagues[11] reported in 1973 that most patients with histologically confirmed TTP had normal or only borderline results for PT, PTT, and the fibrinogen level. At the time, the pathogenesis of TTP was unknown and the authors were trying to determine if DIC had a role in it. A few years later, Neame et al[12] concluded that severe thrombocytopenia, a normal fibrinogen concentration, and normal to mildly elevated fibrin degradation products (which include D-dimers) were common findings in TTP. More recently, Sagripanti et al[15] postulated that coagulation activation does not occur in TTP based on normal PT and PTT values. However, their selection criteria included only patients with normal results for these assays. Thus, their findings cannot be directly compared with ours, which included all patients with the clinical diagnosis of TTP-HUS. The same authors, however, noted that all patients with TTP had increased D-dimer concentrations, demonstrating that this assay is more sensitive to identify in vivo activation of the coagulation cascade than PT and PTT.[15] Other studies also concluded that there is thrombin generation in TTP, although to a lesser degree than that in DIC.[13,14] Although these previous reports support our findings, unlike any of these studies, we performed a direct comparison of laboratory results between matched patients with TTP-HUS or DIC treated and tested concurrently at the same institution.

Several studies used more specialized coagulation tests in patients with TTP-HUS, such as prothrombin fragment 1 + 2, thrombin-antithrombin complexes, tissue-type plasminogen activator, plasminogen activator inhibitor-1, plasmin–α_2-antiplasmin complex, tissue factor and tissue factor pathway inhibitor, thrombomodulin, protein C, protein S, and von Willebrand factor.[13-15,18-22] Although the findings were valuable to characterize the underlying pathogenesis of TTP-HUS at the time of publication, the usefulness of these tests remains low owing to the lack of their immediate availability in the acute clinical setting. Thus, unlike the platelet count and PT, they are unlikely to aid in the decision to proceed with TPE. Furthermore, at present, measurement of ADAMTS13 activity has replaced all of them.

Our study has several limitations, which include the relatively small number of patients, lack of ADAMTS13 measurements in all cases, and its retrospective format. However, the sample size is justified by the low incidence of TTP-HUS, and our choice to limit the analysis to a single institution to eliminate the variability of laboratory assay results performed at different sites is a strength. In addition, the retrospective design allowed us to confirm the diagnosis of TTP-HUS based on the patients' response to TPE, result of ADAMTS13 testing when available, and overall clinical assessment for both groups of patients. On the other hand, we believe that the case-control approach added credibility to our findings because a clinical diagnosis of DIC is often the most difficult diagnosis a clinician must exclude when a patient is suspected of having TTP-HUS, especially when fever is present.

We propose that our findings may be quite useful for a variety of physicians in different specialties who evaluate patients with MAHA. Faced with a patient with severe thrombocytopenia and a normal or mildly prolonged PT, arrangements for TPE should be initiated promptly. Although TPE is lifesaving in patients with a high likelihood of TTP-HUS, it is also imperative to remember that the decision to proceed must include the consideration that the perceived benefit outweighs the risks and potential complications.[23] To increase the diagnostic accuracy of TTP, we suggest routine collection of a citrated blood sample for ADAMTS13 activity determination before TPE in all patients suspected of having TTP-HUS.[24] As the result of ADAMTS13 activity becomes available, it should be taken into account in the decision to continue or discontinue TPE along with the clinical situation. Our results suggest a role for routine laboratory assays to help identify patients with TTP-HUS and promptly refer them to lifesaving treatment during the acute presentation.

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