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Measuring ADAMTS13 Activity in Patients with Suspected Thrombotic Thrombocytopenic Purpura: When, How, and Why?

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During the past 17 years, thrombotic thrombocytopenic purpura (TTP) has become defined by a severe deficiency of ADAMTS13.[1] However this definition is not equivalent to a diagnosis of TTP. ADAMTS13 measurements have become common in our evaluation and management of patients with suspected TTP, but there are still uncertainties about the interpretation of these measurements. To address these uncertainties, we need to consider three questions. Addressing these questions is something that clinicians do whenever seeing a patient for whom the question is, "Does she have TTP?"

Question 1. When was the blood sample for measurement of ADAMTS13 activity drawn?

We ask this question because we are concerned about the validity of the results if the blood sample was drawn after PEX was begun. This question is addressed in this issue of *Transfusion* by Wu, et al.[2] in their clear, concise, and clinically important study that begins with the statement, "clarification of the diagnostic and prognostic values of ADAMTS13 activity obtained during PE treatment is an unmet clinical need". Their analysis of patients with acquired autoimmune TTP, whose diagnosis was supported by ADAMTS13 activity <10% plus ADAMTS13 inhibitor activity, documents that most patients (14 [78%] of 18) continue to have ADAMTS13 activity <10% even after three days of PEX. Therefore not only do clinicians have a second chance to measure ADAMTS13 activity, Wu, et al. also document that the recovery, or lack of recovery, of ADAMTS13 activity is related to the patients' clinical outcome. These observations provide immediate support for clinicians.

Question 2. How was ADAMTS13 measured?

We ask this question because we are concerned that all methods of measurement may not be equivalent. Measurement of ADAMTS13 activity may not be as simple and consistent as measurements of, for example, hemoglobin concentration. The answer to this question is disappointing; different methods of measuring ADAMTS13 activity may yield different results. Wu, et al.[2] used a unique mass spectrometry method that was developed in their

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laboratory and is not yet available elsewhere. The rest of us depend on a variety of commercial laboratories. These variable sources make a difference, illustrated by my experience with two patients last year. When hematologists in our community care for a patient with suspected TTP, they order commercially available ADAMTS13 measurements, just as hematologists everywhere do. In addition, as part of our Oklahoma Registry, we collaborate with Dr. Johanna Kremer Hovinga and her colleagues (University of Bern, Switzerland) who measure ADAMTS13 activity in each patient by two methods, immunoblotting of degraded von Willebrand factor (VWF) and a fluorogenic assay using FRETS-VWF73 substrate.[3] Even in this experienced research laboratory, the results between these two methods may vary.[3] These measurements are only a research tool for us; unfortunately, the results aren't available in time for patient management decisions.

Here are the stories of these two patients. I suspected acquired severe ADAMTS13 deficiency in both women. In Patient 1, the commercial ADAMTS13 results was 20%; I was surprised. Then later the Swiss results were: immunoblot, 10%; FRETS, 7%; FRETS inhibitor, 0.5 Bethesda units. I then felt that my clinical judgment had been confirmed, that she had acquired autoimmune TTP and required careful follow-up for long-term risks including risk for relapse.[4] In Patient 2, the commercial ADAMTS13 results was 9%; I was not surprised. Then later the Swiss results were: immunoblot, 20%; FRETS, 28%. I still think she had acquired, autoimmune TTP. She had a prolonged clinical course, ultimately responding to treatment with rituximab in addition to PEX and corticosteroids. These two patients illustrate the potential for patient management errors if clinical decisions are based only on the results of ADAMTS13 activity measurements. Rigid adherence to a single laboratory test value would have been misleading in both cases.

Question 3. How should the results of the ADAMTS13 measurement be used for patient management decisions?

This question leads to many other questions. What level of ADAMTS13 activity defines a “severe” deficiency? How sensitive and specific is severe ADAMTS13 deficiency for the diagnosis of TTP? Can patients have TTP without a severe deficiency of ADAMTS13? Can patients without TTP (for example, systemic infection or malignancy) have a severe deficiency of ADAMTS13? Is it appropriate to use the level of ADAMTS13 activity alone to establish or exclude the diagnosis of TTP and therefore to begin or not begin treatment with PEX?

Using the data from our Swiss measurements, we set an arbitrary ADAMTS13 activity level of less than 10% (by either of the two methods) to define a severe deficiency and therefore to support (not “to make”) the diagnosis of TTP.[3] This level included almost all patients who had relapsed episodes and therefore we deemed it to beclinically relevant. Also this level excluded almost all patients who had an alternative diagnosis, such as a systemic infection or malignancy. Of course the phrase “almost all patients” is a critical element in these sentences.

For example, our experience includes a man whose clinical course and long-term outcomes were characteristic of relapsing acquired autoimmune TTP, yet he had normal ADAMTS13

deficiency when he initially presented (53% and 60% by the two Swiss assays). With each relapse his ADAMTS13 activity was less. He developed undetectable ADAMTS13 activity with a demonstrable inhibitor with his fifth and sixth episodes. We concluded that anti-ADAMTS13 antibodies may be important *in vivo* despite normal ADAMTS13 activity *in vitro*.[5] For this patient, treatment with PEX for TTP was essential in spite of the results of the initial ADAMTS13 measurements.

Our experience also includes a woman who was initially treated with PEX for suspected TTP but whose clinical, laboratory, and imaging evaluations all subsequently documented the diagnosis of acute bacterial endocarditis caused by *Staphylococcus epidermidis*, apparently excluding the diagnosis of TTP. Later we learned that her ADAMTS13 activity was undetectable by both the immunoblot and FRETS assays.[6] For this patient, treatment with plasma exchange may have been unnecessary, in spite of severe ADAMTS13 deficiency.

Therefore our experience suggests that the dominant criterion for initiating or discontinuing PEX should be the absence or presence of an alternative etiology for the microangiopathic hemolytic anemia and thrombocytopenia. I believe that this critical initial management decision should not be based merely on the level of ADAMTS13 activity, as has been recently suggested.[7] If an alternative etiology is not apparent, it is appropriate to begin and continue PEX even if the ADAMTS13 activity is not severely deficient. If an alternative etiology is apparent, it may be appropriate to hesitate before beginning PEX and to observe the patient's clinical course and response to appropriate treatments. If an alternative etiology becomes apparent after PEX is begun, it may be appropriate to stop the PEX and focus on management of the alternative etiology. This practice is consistent with the randomized clinical trial that first documented the efficacy of PEX for treatment of TTP, performed in the era preceding the discovery of ADAMTS13, when management decisions were based only on the clinical evaluation.[8]

The presence of severe ADAMTS13 deficiency supports the clinical diagnosis of TTP but ADAMTS13 activity values alone neither establish nor exclude the diagnosis of TTP. The role of ADAMTS13 measurements in the management of patients with suspected TTP is not the same as the role of pathology in the management of patients with suspected cancer. In oncology, pathology rules. In the management of patients with suspected TTP, the clinician continues to rule. ADAMTS13 measurements certainly help, and the data or Wu, et al.[2] tell us how ADAMTS13 measurements can be even more helpful. But even now, in 2015, management of patients with suspected TTP remains the responsibility of the clinician.

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