

## ADAMTS13 Activity

### Introduction

ADAMTS13 (a disintegrin and metalloprotease with thrombospondin-1-like motif, member 13), also referred to as VWF-cleaving protease, is a metalloprotease that cleaves von Willebrand factor (VWF).<sup>1</sup> VWF is secreted from endothelial cells as unusually large multimers that bind platelets excessively unless cleaved by ADAMTS13. Hereditary or acquired deficiency of ADAMTS13 may lead to excessive platelet aggregation, causing microvascular platelet-rich thrombi, a clinical condition referred to as thrombotic thrombocytopenic purpura (TTP).<sup>1</sup> Clinically, TTP is characterized by the presence of microangiopathic hemolytic anemia (MAHA) and thrombocytopenia, typically accompanied by neurologic abnormalities or other signs of organ injury.<sup>2</sup> Measurement of ADAMTS13 activity in the laboratory is a critical component in the diagnostic and treatment algorithm of patients presenting with acute thrombotic microangiopathy.<sup>3</sup>

### Laboratory Method

In LabCorp's liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay, ADAMTS13 activity is determined by measuring the cleavage of a synthetic polypeptide substrate (referred to as VWF73<sup>4</sup>) added to plasma samples. The amino acid sequence of VWF73 corresponds to amino acid residues 1596 through 1668 of mature VWF and, thereby, possesses the tyrosine-methionine cleavage site and exosite necessary to undergo specific cleavage by plasma ADAMTS13.<sup>5</sup> Using LC-MS/MS, cleavage of VWF73 is determined directly by measuring a specific proteolytic product of VWF73 whose quantity is directly proportional to the activity of ADAMTS13 in plasma.

The new LC-MS/MS assay for measuring ADAMTS13 activity is traceable to the WHO 1st International Standard for ADAMTS13<sup>6</sup> to ensure accurate measurements and offers several advantages relative to comparable fluorescence-based assays:

- **Improved sensitivity** — LabCorp's LC-MS/MS assay has a reportable range extending down to 2% of normal activity, which is a marked improvement relative to fluorescence-based assays. Given that low levels of ADAMTS13 activity are an indication of thrombotic thrombocytopenic purpura (TTP),<sup>7</sup> the ability to accurately measure ADAMTS13 to below 5% improves the utility of this assay, particularly as ADAMTS13 activity less than 10% is extremely rare except in cases of TTP, and severe deficiency is sometimes defined as less than 5%.<sup>8,9</sup>
- **Improved repeatability** — In a comparative study of individual samples repeated across multiple days by both LabCorp's LC-MS/MS assay and a commercially available fluorescence-based assay, the median CV by the LC-MS/MS assay was 7.1% as compared to 21.8% by the fluorescence-based assay.<sup>10</sup> Improved repeatability of ADAMTS13 activity measurements should improve the management of patients with suspected TTP, particularly when monitoring ADAMTS13 activity during the course of total plasma exchange therapy.
- **Reduced Interference** — Fluorescence-based assays have been shown to be susceptible to interferences from hyperbilirubinemia<sup>11</sup>; however, LabCorp's LC-MS/MS assay has been demonstrated to be accurate in the presence of up to 20 mg/dL bilirubin, which should reduce rejection rate of samples submitted for ADAMTS13 activity testing and eliminate the potential for falsely low activity measurements due to hyperbilirubinemia.

**Reduced Turnaround Time (TAT)** — Given the efficiency of LabCorp's LC-MS/MS assay, a rapid TAT is available. LabCorp sets this assay up every day (seven days a week). Samples received in the Burlington, NC laboratory before 10:30 AM EST will be reported by 6:00 PM on the same day. A reduction in TAT for ADAMTS13 testing has been shown to be critical in management of patients with suspected (TTP) by reducing unnecessary plasma exchange therapy and improving efficiency of patient care.<sup>12</sup> Eliminating unnecessary plasma exchange therapy not only has implications for cost reduction, but may also prevent the potentially harmful effects associated with the therapy.<sup>13</sup>

## Clinical Application

Thrombotic microangiopathy (TMA) refers to occlusive microvascular thromboses, which leads to MAHA, thrombocytopenia, and varying degrees of organ injury. These clinical findings may be seen in primary TMAs, or as secondary findings in various clinical conditions, such as systemic infection, cancer, HELLP syndrome, severe hypertension, and autoimmune disorders.<sup>2</sup>

Primary TMAs include: TTP, atypical hemolytic-uremic syndrome (aHUS), shiga-toxin mediated TTP (ST-HUS), and drug-mediated TMA.<sup>2</sup> Because these conditions each present with MAHA and thrombocytopenia, distinguishing between the underlying causes can present a clinical challenge. However, as specific treatments have been developed, the need for diagnostic accuracy is increased.

Successful treatment of TTP relies on prompt replacement of ADAMTS13, typically through plasma exchange therapy, which is often initiated as soon as the diagnosis of TTP is suspected. The diagnosis of ADAMTS13 deficiency is supported by ADAMTS13 activity levels that are typically less than 5% to 15%.<sup>2,3,9</sup>

Due to the availability of the complement inhibitor therapy eculizumab for treatment of complement-mediated TMA (aHUS), the need for rapid documentation of ADAMTS13 levels has become increasingly important. Indeed, rapid turnaround time of ADAMTS13 testing has been shown to reduce the number of plasma exchanges, as well as reduce plasma utilization, in patients suspected of having TTP.<sup>12</sup> Thus, prompt evaluation of ADAMTS13 activity can be a critical component of the diagnostic/treatment algorithm for suspected acute TMA.<sup>3,13</sup>

## Relevant Assays

Test No.	Test Name
117913	ADAMTS13 Activity
117921	ADAMTS13 Activity Reflex Profile
117915	ADAMTS13 Antibody

\*For the most current information regarding test options, including specimen requirements and CPT codes, please consult the online Test Menu at [www.LabCorp.com](http://www.LabCorp.com).

### References

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