ADAMTS13 Evaluation:
Activity, Inhibitor, and Antibody

Thrombotic thrombocytopenic purpura (TTP) is a rare life-threatening condition characterized by consumption of platelets, hemolytic anemia, and varying degrees of organ dysfunction. The diagnosis and differentiation of TTP from other thrombotic microangiopathies is often difficult.[1,2]
Versiti's Hemostasis Reference Laboratory offers comprehensive testing for ADAMTS13 and clinical diagnosis of TTP.

ADAMTS13 is a plasma protein that cleaves von Willebrand factor, regulating the interaction of platelets with VWF. Absent or low ADAMTS13 activity allows formation of platelet microthrombi, which in turn obstruct arterioles and capillaries, generating the clinical sequelae of TTP. ADAMTS13 activity <10% supports a diagnosis of TTP.

The majority of adults with idiopathic TTP have a severe deficiency of ADAMTS13 with activity levels <10%.[1,2] The low levels are often due to autoantibodies that inhibit or clear ADAMTS13. Patients with idiopathic TTP usually require therapeutic plasma exchange to achieve clinical remission.[2,3] Patients with idiopathic TTP and severe ADAMTS13 deficiency are more likely to respond to plasma exchange therapy than patients without severe deficiency. Persistence of ADAMTS13 deficiency or an inhibitor/antibody during clinical remission suggests an increased risk for recurrence of symptomatic TTP.[2,4-6] Identification of an autoimmune mechanism in idiopathic TTP explains the rationale for immunotherapy.[1,2]

Congenital severe ADAMTS13 deficiency is an autosomal recessive disorder (Upshaw-Schulman syndrome). Patients may present as children or adults, and are at risk for recurrent episodes of TTP. Antibody to ADAMTS13 is usually not detected and patients generally improve with plasma transfusion therapy for ADAMTS13 replacement.

Reflex algorithm: ADAMTS13 Evaluation is a reflexive testing algorithm. ADAMTS13 Activity is always performed. If activity is ≤ 30%, the inhibitor assay is performed. If the inhibitor is ≤ 0.7 Inhibitor Units, testing for ADAMTS13 Antibody is performed. Charges reflect assays performed. Each test is available for individual order.

Indications for testing:

- Test results may assist in diagnosis of congenital or idiopathic TTP, and may have prognostic value regarding likelihood of relapse.[1,2,4,5]
- Severe deficiency of <10% appears to be a relatively specific finding in patients with a clinical diagnosis of idiopathic TTP or Upshaw-Schulman syndrome.
- Low activity with inhibitor/antibody has increased specificity for idiopathic TTP.

Test method:

ADAMTS13 activity is measured by Fluorescence Resonance Energy Transfer (FRET) with a synthetic substrate.[7] ADAMTS13 inhibitor is determined using mixing studies; one inhibitor unit is defined as the concentration of inhibitor able to reduce the ADAMTS13 activity of an equal volume of normal pooled plasma by half.[8] The ADAMTS13 antibody assay detects IgG antibody serologically by ELISA.

Assay sensitivity and limitations:

- Not all patients with idiopathic TTP have abnormal ADAMTS13 laboratory results. The reported prevalence of severe deficiency in patients presenting with idiopathic TTP varies from 33 to 100%.[1,2] Prevalence of inhibitors 44% to 93%6,8 with a somewhat higher reported prevalence of antibody detected by ELISA.

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- Severe deficiency of ADAMTS13 has been proposed as a relatively specific laboratory marker of TTP. Whether severe deficiency occurs in other conditions is debated.[5] Mild to moderate deficiency has been observed in multiple medical conditions including inflammation, hepatic dysfunction and pregnancy.[1]
- Recent plasma exchange therapy may affect ADAMTS13 assay findings.
- Hemolysis with plasma free hemoglobin >2 gm/L or an elevated bilirubin level can cause artifactually low ADAMTS13 activity and false positive inhibitor results.[9]
- ADAMTS13 Antibody assay is less specific than the functional inhibitor assay, and positive results have been observed in people without severe ADAMTS13 deficiency, including healthy individuals and patients with other immunologic disorders.[6]

Reporting of results:

ADAMTS13 Activity: ≥ 67%

ADAMTS13 Inhibitor: ≤ 0.4 Inhibitor Unit

ADAMTS13 Antibody: ≤ 18 Arbitrary Units

Specimen requirements:

Citrated plasma, frozen in plastic tubes

ADAMTS13 Evaluation: 3 aliquots (0.5 ml each)

ADAMTS13 Activity or Inhibitor or Antibody:
0.5 ml for each test ordered

SHIP

Shipping requirements:

Place the frozen specimen and the test requisition form into plastic bags, seal and place in an insulated container. Surround with at least 5 pounds of dry ice. Seal the insulated container, place in a sturdy cardboard box and tape securely. Ship the package in compliance with your overnight carrier guidelines. Label with the following address:

Versiti Client Services
Hemostasis Reference Laboratory
638 N. 18th Street
Milwaukee, WI 53233
800-245-3117, ext. 6129

ORDER

Required forms:

Please complete all pages of the requisition form.

CPT Codes/Billing/Turnaround time:

Test code: 1295

CPT codes:

ADAMTS13 Activity: 85397

ADAMTS13 Inhibitor: 85335

ADAMTS13 Antibody: 83520

Turnaround time:

ADAMTS13 Activity and Inhibitor: 3-4 Days

ADAMTS13 Antibody: 7-10 Days

References:

1. Sadler JE. Von Willebrand Factor, ADAMTS13 and thrombotic thrombocytopenic purpura. Blood 2008:112:11-18.
2. Hovinga JA, Meyer SC. Current management of thrombotic thrombocytopenic purpura. Curr Opin Hematol 2008;15:445-450.
3. Rock GA, Shumak KH, Buskard NA, et al. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura: Canadian Apheresis Study Group. N Engl J Med 1991;325:393-397.
4. Peyvandi F, Lavoretano S, Palla R, et al. ADAMTS13 and anti-ADAMTS13 antibodies as markers for recurrence of acquired thrombotic thrombocytopenic purpura during remission. Haematologica 2008;93:232-9.
5. Laemmle B, Kremer Hovinga JA, George JN. Acquired thrombotic thrombocytopenic purpura: ADAMTS13 activity, anti-ADAMTS13 autoantibodies and risk of recurrent disease. Haematologica 2008;93:172-177.
6. Rieger M, Mannucci PM, Kremer Hovinga JA, et al. ADAMTS13 autoantibodies in patients with thrombotic microangiopathies and other immunomediated diseases. Blood 2005; 106:1262-1267.
7. Kokame K, Nobe Y, Kokubo Y, et al. FRETS-VWF73, a first fluorogenic substrate for ADAMTS13 assay. Br. J.Haematol 2005;129:93-100.
8. Zheng XL, Kaufman RM, Goodnough LT, Sadler JE. Effect of plasma exchange on plasma ADAMTS13 metalloprotease activity, inhibitor level, and clinical outcome in patients with idiopathic and nonidiopathic thrombotic thrombocytopenic purpura. Blood 2004;103: 4043-4049.
9. Studt J-D, Kremer Hovinga JA, Antoine G, et al. Fatal congenital thrombotic thrombocytopenic purpura with apparent ADAMTS13 inhibitor: in vitro inhibition of ADAMTS13 activity by hemoglobin. Blood 2005;105;542-544.

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